

Yale University

EliScholar – A Digital Platform for Scholarly Publishing at Yale

Yale School of Medicine Physician Associate
Program Theses

School of Medicine

5-1-2019

Early, Proactive Palliative Care in Hospitalized Patients with Advanced Dementia: A Research Proposal

Tori Viveen

Yale Physician Associate Program, victoriaviveen@gmail.com

Follow this and additional works at: https://elischolar.library.yale.edu/ysmpa_theses



Part of the [Medicine and Health Sciences Commons](#)

Recommended Citation

Viveen, Tori, "Early, Proactive Palliative Care in Hospitalized Patients with Advanced Dementia: A Research Proposal" (2019). *Yale School of Medicine Physician Associate Program Theses*. 55.
https://elischolar.library.yale.edu/ysmpa_theses/55

This Open Access Thesis is brought to you for free and open access by the School of Medicine at EliScholar – A Digital Platform for Scholarly Publishing at Yale. It has been accepted for inclusion in Yale School of Medicine Physician Associate Program Theses by an authorized administrator of EliScholar – A Digital Platform for Scholarly Publishing at Yale. For more information, please contact elischolar@yale.edu.

EARLY, PROACTIVE PALLIATIVE CARE IN HOSPITALIZED PATIENTS WITH
ADVANCED DEMENTIA: A RESEARCH PROPOSAL

A Thesis Presented to
The Faculty of the School of Medicine
Yale University

In Candidacy for the degree of
Master of Medical Science

May 2019

Tori Viveen, PA-SII
Class of 2019
Yale Physician Associate Program

Kathleen Akgün, MD
Associate Professor
YSM Medical Intensive Care Unit

Table of Contents

LIST OF TABLES/FIGURES.....	IV
LIST OF ABBREVIATIONS.....	IV
ABSTRACT	V
CHAPTER 1: INTRODUCTION	1
1.1 BACKGROUND	1
1.1.1 Dementia.....	1
1.1.2 Palliative Care:.....	6
1.1.3 Palliative Care and Dementia:	9
1.2 STATEMENT OF THE PROBLEM.....	12
1.3 GOALS AND OBJECTIVES	13
1.4 HYPOTHESIS	13
1.5 REFERENCES	13
CHAPTER 2: REVIEW OF THE LITERATURE	15
2.1 INTRODUCTION	15
2.2 PROOF OF CONCEPT - ADVANCED DEMENTIA & UNMET PALLIATIVE CARE NEEDS	15
2.3 REVIEW OF EMPIRICAL STUDIES.....	18
2.3.1 Palliative Care as an Intervention to Improve Outcomes in Chronic Diseases.....	18
2.3.2 Palliative Care as an Intervention to Improve Outcomes in Advanced Dementia.....	21
2.4 POTENTIAL CONFOUNDING VARIABLES	26
2.5 REVIEW OF RELEVANT METHODOLOGY	28
2.5.1 Study Design	28
2.5.2 Selection Criteria.....	29
2.5.3 Intervention.....	31
2.5.4 Outcome Measures	32
2.5.5 Sample Size	33
2.6 CONCLUSION.....	36
2.7 REFERENCES	36
CHAPTER 3: METHODS.....	40
3.1 STUDY DESIGN.....	40
3.2 STUDY POPULATION AND SAMPLING.....	40
3.3 PARTICIPANT PROTECTION AND CONFIDENTIALITY	42
3.4 STUDY VARIABLES AND MEASURES.....	43
3.5 METHODOLOGY	44
3.5.1 Assignment of Intervention	44
3.5.2 Intervention.....	44
3.5.3 Adherence	45
3.6 DATA COLLECTION	45
3.7 SAMPLE SIZE CALCULATION	45
3.8 ANALYSIS.....	46
3.9 TIMELINE AND RESOURCES	47
3.10 REFERENCES	48
CHAPTER 4: CONCLUSION	49
4.1 ADVANTAGES AND DISADVANTAGES	49
4.2 CLINICAL SIGNIFICANCE	50
4.3 REFERENCES:	50
APPENDICES	51
APPENDIX A: COMPOUND CONSENT FORM AND PRIVACY RULE AUTHORIZATION FORM.....	51

APPENDIX B: BASELINE CHARACTERISTICS FORM	55
APPENDIX C: FOLLOW-UP DATA COLLECTION SHEET	56
APPENDIX D: HOSPITAL ANXIETY AND DEPRESSION SURVEY	57
APPENDIX E: SAMPLE SIZE CALCULATION.....	58
APPENDIX F: FUNCTIONAL ASSESSMENT SCALE	59
APPENDIX G: DSM-V DEMENTIA-MAJOR NEUROCOGNITIVE DISORDER CRITERIA.....	60
BIBLIOGRAPHY	61

List of Tables/Figures

In order of appearance:	
Figure 1	Evidence based domains of high-quality palliative care
Figure 2	Individualized integrated model of palliative care
Table 1	Components of a Palliative Care Consultation
Table 2	Summary of Studies used to calculate sample size
Table 3	Literature-supported primary outcome estimate
Table 4	Inclusion and Exclusion Criteria
Table 5	Dementia ICD-10-CM Codes
Table 6	Proposed Timeline

List of Abbreviations

AD	Alzheimer's Disease
ADL	Activity of Daily Living
COPD	Chronic Obstructive Pulmonary Disease
CT	Computed tomography scan
DSM-5	Fifth edition of the Diagnostic and Statistical Manual of Mental Disorders
EMR	Electronic Medical Record
FAST	Functional Assessment Staging Tool
GDS	Global Deterioration Scale
HADS	Hospital Anxiety and Depression Scale
ICD-10-CM	International Classification of Diseases and Related Health Problems, 10 th Revision, Clinical Modification
MMSE	Mini-Mental State Exam
MoCA	Montreal Cognitive Assessment
MRI	Magnetic Resonance Imaging
PCC	Palliative Care Consultation
RCT	Randomized Controlled Trial
SDM	Surrogate Decision Maker
VA	Veterans Affairs
WHO	World Health Organization

Abstract

Dementia is a chronic, progressive and fatal neurodegenerative disease with no curative treatment options. The number of Americans living with dementia is expected to triple between 2018 and 2050. Access to palliative care for patients living with dementia and other chronic diseases like cancer improves quality of life and may even prolong life. However, the optimal timing for a palliative care consult is not yet clear. This study seeks to determine whether early initiation of palliative care in dementia patients admitted to the hospital with acute illness benefits patient clinical outcomes (non-institutionalized days at home, readmissions, location of death) and psychological distress of surrogate decision makers. We propose a randomized controlled trial of early, proactive palliative care in hospitalized advanced dementia patients. These results may help to improve care for the growing population of older Americans and provide insights into alleviating the suffering of those living with dementia.

CHAPTER 1: INTRODUCTION

1.1 BACKGROUND

According to the 2016 “Aging in the United States” report by the Population Reference Bureau, the number of Americans age 65 and older is expected to more than double from 46 million in 2016 to over 98 million by 2060.¹ As the U.S. population ages, the number of Americans living with Alzheimer’s, a subtype of dementia, is expected to triple between 2018 and 2050.¹ The World Health Organization (WHO) has named dementia as the seventh leading cause of death worldwide, and deaths due to dementias more than doubled between 2000 and 2015.² In the face of an aging population with an increasing prevalence of dementia, the US healthcare system must adapt in response and in preparation.

Palliative care represents a potentially effective intervention for the growing number of older adults living with dementia. Palliative care has been shown to increase favorable outcomes like quality of life in patients living with chronic diseases such as cancer, heart failure and chronic obstructive pulmonary disease (COPD). Palliative care is not restricted to end of life care; it can be delivered beginning at the time of diagnosis of a disease. Early initiation of palliative care is vital for patients suffering with protracted and insidious diseases like dementia that can subsist for years. However, patients living with advanced dementia often are not referred to palliative care, and receive poorer quality of end-of-life care when compared to other terminally-ill patients.

1.1.1 Dementia:

Dementia is a chronic, progressive and ultimately fatal neurodegenerative disease with several different causes and no curative treatment options. Dementia is a disorder

characterized by a decline in cognition involving one or more cognitive domains (learning and memory, executive function, complex attention, perceptual-motor, and social cognition).³ The change in cognition must represent a decline from the previous level of function, interfere with daily function, and inhibit independence.³ Most dementia is caused by a neurodegenerative disease, though there are non-neurodegenerative etiologies as well. The most common neurodegenerative conditions include Alzheimer disease (AD), Dementia with Lewy bodies, Frontotemporal dementia, and Parkinson disease. Alzheimer's disease is the most common presentation of dementia in the elderly population accounting for 60-80% of cases.⁴ The most common non-neurodegenerative type is vascular dementia, unique in that the progression may be slowed by prevention of secondary ischemic events with blood pressure control and blood thinners, for example. Lifelong alcohol abuse may lead to alcohol-related dementia. Dementia may have more than one cause, particularly in older people with many comorbidities, and must be distinguished from delirium and depression. The coexistence of more than one dementia producing pathology is called mixed dementia, and is most commonly seen as AD and vascular dementia.

Currently, the WHO estimates that there are 50 million people living with dementia worldwide.⁵ The WHO also estimates that there are nearly 10 million new cases every year. The rise in the prevalence of dementia may be due to a combination of elderly adults living longer, an increase in incident cases of dementia, and better detection and diagnosis of dementia.

Clinical Presentation:

In general, patients living with dementia, regardless of cause, experience a gradual decline in cognitive, physical and social ability over months to years.⁵ The patient most often presents with short-term memory forgetfulness, and may also experience increasing difficulty with retaining new information, handling complex tasks, and maintaining proficiency in spatial ability and orientation, and language. Examples include forgetting a recent conversation with a loved one, making mistakes in daily medication management, and losing the ability to make a meal. Safety issues may present secondary to cognitive changes; for example, getting lost or leaving the stove on. Physical decline may begin as gait imbalance and progress to something as severe as being unable to lift their head from the pillow in advanced dementia. Socially, people living with dementia begin to withdraw from situations they were previously interested in.

Different varieties of dementia present with distinctive, although generally nonspecific, patterns of cognitive impairment and neurologic manifestations. In contrast, deficits in memory and cognitive function associated with normal aging are often not progressive and do not regularly interfere with daily function. While specific aspects of each type of dementia will be reviewed later, generally shared aspects of each condition are worth noting. The AD syndrome often presents in an adult over the age of 65 with increasing memory impairment, followed by impaired executive function and reduced insight into his or her cognitive dysfunction. These impairments progress to include behavioral and psychologic symptoms such as aggression, depression or psychosis, and sleep disturbance.⁵ Vascular dementia syndrome often presents as prominent impairments in executive function and processing speed, and evidence of vascular disease on brain

magnetic resonance imaging (MRI). Lewy body dementia and Parkinson disease dementia are characterized by a gradual decline in cognitive abilities that is accompanied by motor parkinsonism. As dementia progresses, patients frequently experience a wide array of signs, symptoms and changes resulting in loss of independence.

Advanced or end-stage dementia is characterized by profound cognitive impairment and the inability to verbally communicate. Patients also progress to complete functional dependence secondary to issues like dysphagia and double incontinence.⁵

Advanced dementia is a terminal condition characterized by progressive and persistently severe disability during the last year of life.

Evaluation:

Evaluation for the diagnosis of dementia must be made over a span of at least six months to a year. The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria for diagnosis of dementia (now called major neurocognitive disorder) is included in the appendix (Appendix G). Evaluations for patients with suspected dementia include a complete history and physical, neurologic exam, laboratory and imaging studies. Cognitive testing of with screening tools like the Mini-Mental Status Examination (MMSE) or Montreal Cognitive Assessment (MoCA), or formal neuropsychologic testing are also important to make the diagnosis. The assessed domains include attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. These tools are most helpful when repeated overtime, as patients' baseline cognitive status varies. A diagnosis is ideally made after evaluating for other explanations for neurocognitive impairments such as new medications, drug interactions and/or indolent infections that

may be common in older persons. All patients with suspected dementia should also be screened for depression with a tool like the Patient Health Questionnaire 2, because depression may mimic dementia presentation.

After cognitive testing, laboratory tests should screen for vitamin B12 deficiency, hypothyroidism, and neurosyphilis. Substance use etiologies like opioids or cannabis may cause cognitive impairment and are screened for with a thorough history-taking to determine use patterns and urine or serum toxicology test. Neuroimaging with a head computed tomography scan (CT) or MRI is indicated in patients with acute onset of cognitive impairment, rapid neurologic deterioration or physical exam findings suggestive of subdural hematoma, thrombotic stroke, or cerebral hemorrhage.

After a confirmed diagnosis of dementia, advanced dementia is typically staged with a validated tool like the Functional Assessment Staging Test (FAST). FAST considers early functional losses like name recall, deficits in occupational and social settings, and difficulty with activities of daily living (ADLs). Later stage considerations include presence of urine and stool incontinence, limits in speech and vocabulary, and ultimately the ability to move or react.⁶ The scale ranges from 1 with no objective or subjective functional decrement, to 7f with the inability to hold one's head up (Appendix F).⁶

Prognosis and Treatment:

In dementia, the prognosis and trajectory of disease is often unpredictable and indolent. In the absence of a significant comorbidity, the mean time from diagnosis to death depends on age at dementia diagnosis. For example, time to death for those diagnosed at age 65-70 is 8.3 years, and for those diagnosed at age 90 is 3.4 years.⁷ For

people with advanced dementia, reported six-month mortality rates are 25%, comparable to mortality rates of people with other conditions regarded as terminal.⁸⁻¹⁰ Unlike other terminal conditions, advanced dementia is characterized by a gradual decline in function over an extended period, without abrupt functional or physical health changes that clearly identify the terminal phase of the disease.⁵

As the overall population ages worldwide, dementia will become more and more prevalent. Advances in the understanding of dementia and its subtypes have changed the management of dementia from conservative and symptomatic, to more specific biologically-based treatment, which is not discussed in this study proposal. There may also be a role for concurrent cognitive rehabilitation in patients in the early stages of dementia to maintain memory and higher cognitive function. During the early stages of dementia, it is also important to discuss shared decision making and advanced care planning, as the progression of the disease is unpredictable. This is essential because in later stages patients may be unable to express their preferences about invasive medical treatment and the transition to end-of-life care. In patients with advanced dementia, clinicians should focus on compassionate, evidence-based care aligned with patient and surrogate decision maker (SDM) preferences. Especially in populations with advanced dementia, palliative rather than curative care is essential to maximize comfort and quality of life.

1.1.2 Palliative Care:

The World Health Organization defines palliative care as:

“a [team] approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention

and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual.”¹¹

Palliative care teams may help address a wide array of concerns and facilitate difficult treatment decisions at any stage of a disease. Evidence-based domains of high-quality palliative care can be delivered with an interdisciplinary team and concurrently with active medical therapies (Figure 1).¹²



Figure 1: Evidence based domains of high-quality palliative care.

Palliative Care vs. Hospice:

In some countries, the terms hospice and palliative care are used interchangeably. As palliative care has evolved, treatment of physical, emotional and spiritual suffering from the time of illness diagnosis is encouraged—rather than solely at the end of life. The Center to Advance Palliative Care defines the expanding role of palliative care as

“specialized medical care for people living with serious illness—whatever the diagnosis. The goal is to improve quality of life for both the patient and the family.”¹³ Palliative care can be utilized as an extra layer of support from the time of diagnosis, throughout treatment, and alongside as patients and families transition to hospice care and death. Specific clarification of palliative medicine vs. hospice care are partially determined by insurance coverage but also depend on time to end of life care (Figure 2). The patient may begin to receive palliative care at diagnosis and concurrently with disease modifying therapy. An individualized approach modifies treatment to reflect the needs and preferences of the patient, family, caregivers and surrogate decision makers. Palliative care encompasses hospice care for the patient and bereavement support for the family.



Figure 2: Individualized integrated model of palliative care.

History:

The foundation for modern palliative care services is owed largely to the work of Dame Cicely Saunders throughout the 1950s and 1960s.¹⁴ Saunders recognized the multi-dimensional nature of suffering through the concept of “total pain” and the need for emotional, psychological and spiritual support of both the terminally ill patient and their

caregivers.¹⁴ She sought a new approach to “total pain” and symptom management: the basis of modern palliative care.

In the wake of this movement, a strong collaboration of volunteers, nurses, chaplains, psychosocial professionals and physicians shared a concern for how the health care system was “caring—or more accurately, not caring—for the dying.”¹⁵ This collaboration grew to form the first large National Hospice Organization (NHO) conference in Washington, D.C. in 1978 where the first Standards of a Hospice Program of Care was published.¹⁵ In 1999, the NHO changed its name to the National Hospice and Palliative Care Organization (NHPCO) as a reflection of the development of palliative care as a distinct specialty.¹⁵

Providers recognized that palliative care was needed for patients who were not yet terminally ill, yet had serious illnesses with difficulty controlling symptoms. To meet these needs, specialist palliative care in the US has grown dramatically in the past half-century. The Center to Advance Palliative Care reports that the number of palliative care programs increased from 15% of hospitals in 2000 to 30% of hospitals in 2006—a 96% increase in five years.¹⁵ More than 40 years have passed since the introduction of palliative care in the United States; beginning as a small movement, palliative care has now evolved into a large health care specialty.¹⁵

1.1.3 Palliative Care and Dementia:

Traditionally, palliative care has been associated closely with oncology (treating patients living with cancer); however, in the past decade there has been a worldwide call to increase evidence of the benefits and access to palliative care for all people living with

other life-limiting illnesses.⁵ In conditions with prolonged courses like heart failure or COPD, studies on palliative care have proved successful.

There is growing evidence that people with dementia will benefit from palliative care, like other chronic diseases, in ways such as improved quality of life and reduced readmissions and length of stay. A recent systematic review suggests that palliative care should be initiated as soon as possible and integrated into the daily care of people living with dementia.¹⁶ Critical moments to initiate palliative care may include the time of dementia diagnosis, or when changes occur in the health status, place of residence or financial situation.¹⁶ Due to the disease's progressive nature, an early start to palliative care may optimize patient involvement in palliative care and end-of-life decision making while cognitive decline is still mild. Early and continuous palliative care intervention may help patients with more insidious courses of dementia to receive optimal care with hospitalization for other illnesses.¹⁷ Like in other well-studied populations, providing high quality palliative care for people with dementia and their caregivers requires advanced care planning, discussion of comfort care, and preparation for the dying and grieving process.

For people living with dementia, decision-making capacity decreases as the severity of the disease increases.¹⁸ Consequently, it becomes harder to make important life decisions that affect lifestyle, medical treatment, and end-of-life care. This responsibility is often given to someone else—a surrogate decision maker. A surrogate decision maker may be legally appointed (legal guardian, power of attorney) or a family member or caregiver. The role of a surrogate decision maker represents substituted judgement for the patient in the absence of first-hand knowledge of the patient's

preferences. Transition into the role of surrogate decision maker introduces many stressful ethical issues for the surrogate like how to support the patient's right to make autonomous choices and how best to promote a good quality of life for the patient. Particularly distressing situations involve end-of-life care decision-making. Anxiety, depression, and post-traumatic stress are common symptoms experienced by surrogate decision makers.¹⁹ Current literature calls for interventions to support surrogates throughout the decision-making process so that negative psychological symptoms may be avoided.¹⁹ The field of palliative care is dedicated to supporting surrogate decision makers in their role through assistance with medical decision-making and advance care planning.

Despite the wide-spread understanding that palliative care may be beneficial for patients suffering with dementia and their surrogate decision makers, these patients are often going without the necessary palliative support. Patients with advanced dementia may be receiving different end-of-life care to people without cognitive impairment, as well as having less access to palliative care specialists.²⁰ For example, one study of 68,091 participants found that patients dying from Alzheimer's disease and other types of dementia receive a poorer quality of end-of-life care when compared to patients dying from cancer.²¹ Additionally, for patients with advanced dementia (who have gradually lost the ability to make informed decisions on their own), palliative care discussions on advanced care planning are lacking compared to other populations living with chronic disease.¹⁶ Advanced care planning is essential for smooth, end-of-life care preparation and informed surrogate decision making to ensure compliance with the patient's preferences when they are no longer able to contribute to the conversation. Some studies

suggest that this lack of appropriate treatment and advanced care planning is caused by a poor understanding of the “end-phase” of dementia.

While many studies have begun to explore this relationship, a Cochrane systematic review from 2016 found that “very little high-quality work has been completed exploring palliative care interventions in advanced dementia.”⁵ A study of palliative care interventions in acutely-hospitalized patients with advanced dementia and their surrogate decision makers is relevant and necessary due to the ever-increasing population of people living with dementia and the significant suffering it causes. As this proposed trial elucidates, there is an urgent need for palliative care provision for people with advanced dementia and their surrogates to offer support through the end-stage journey with dementia.

1.2 STATEMENT OF THE PROBLEM

Developing and delivering appropriate, timely palliative care to the growing population of people in the US living and dying with dementia is an issue of critical clinical and public health importance. Those living with advanced dementia are a particularly important population because studies have demonstrated that they are subject to unnecessary testing, life-sustaining treatments and transitions of care during the end stage of their illness.²⁰ Palliative care has been proven in other patient populations to increase patient and family satisfaction, maximize number of days spent at home, and improve quality of life. Patients with dementia are less likely to receive palliative care consultations.⁵ To improve the quality of life of patients living with advanced dementia

and to improve the support for surrogate decision makers, further research for evidence-based palliative care interventions in patients with advanced dementia is needed.

1.3 GOALS AND OBJECTIVES

We propose to investigate whether a proactive, inpatient palliative care consultation for patients with advanced dementia significantly increases 6-month non-institutionalized, home days. Secondary outcomes will examine the effect of a palliative care consultation on number of readmissions within the follow-up period, location of death among decedents, and surrogate decision maker psychological distress. In doing so, this study aims to add to the existing literature on dementia and palliative care.

1.4 HYPOTHESIS

Among patients with advanced dementia hospitalized with an acute medical problem, those who receive a palliative care consult within 72 hours of admission will have a significantly higher median number of non-institutionalized days in the six months following the palliative care intervention compared to those who receive no palliative care consult during hospital admission.

1.5 REFERENCES

1. Fact Sheet: Aging in the United States – PRB. <https://www.prb.org/aging-unitedstates-fact-sheet/> 2018.
2. Sampson EL, Candy B, Davis S, et al. Living and dying with advanced dementia: A prospective cohort study of symptoms, service use and care at the end of life. *Palliat Med.* 2018;32(3):668-681.
3. *Diagnostic and Statistical Manual of Mental Disorders*. Fifth Edition (DSM-5) ed. Arlington: American Psychiatric Association 2013.

4. Ballard C, Gauthier S, Corbett A, Brayne C, Aarsland D, Jones E. Alzheimer's disease. *Lancet*. 2011;377(9770):1019-1031.
5. Murphy E, Froggatt K, Connolly S, et al. Palliative care interventions in advanced dementia. *Cochrane Database Syst Rev*. 2016;12:CD011513.
6. Sachdev PS, Blacker D, Blazer DG, et al. Classifying neurocognitive disorders: the DSM-5 approach. *Nat Rev Neurol*. 2014;10(11):634-642.
7. Sclan SG, Reisberg B. Functional assessment staging (FAST) in Alzheimer's disease: reliability, validity, and ordinality. *Int Psychogeriatr*. 1992;4 Suppl 1:55-69.
8. Brookmeyer R, Corrada MM, Curriero FC, Kawas C. Survival following a diagnosis of Alzheimer disease. *Arch Neurol*. 2002;59(11):1764-1767.
9. Mitchell SL, Kiely DK, Hamel MB, Park PS, Morris JN, Fries BE. Estimating prognosis for nursing home residents with advanced dementia. *JAMA*. 2004;291(22):2734-2740.
10. Mitchell SL, Teno JM, Kiely DK, et al. The clinical course of advanced dementia. *N Engl J Med*. 2009;361(16):1529-1538.
11. Morrison RS, Siu AL. Survival in end-stage dementia following acute illness. *JAMA*. 2000;284(1):47-52.
12. WHO definition of Palliative Care.
<http://www.who.int/cancer/palliative/definition/en/>, 2018.
13. Akgun KM. Palliative and End-of-Life Care for Patients with Malignancy. *Clin Chest Med*. 2017;38(2):363-376.
14. Kapo JM, Akgun KM. Integrating Palliative Care Into the Care of Patients With Advanced Lung Cancer. *Cancer J*. 2015;21(5):434-439.
15. Connor SR. Development of hospice and palliative care in the United States. *Omega (Westport)*. 2007;56(1):89-99.
16. Brooksbank M. Palliative care: Where have we come from and where are we going? *Pain*. 2009;144(3):233-235.
17. Piers R, Albers G, Gilissen J, et al. Advance care planning in dementia: recommendations for healthcare professionals. *BMC Palliat Care*. 2018;17(1):88.
18. Mogan C, Lloyd-Williams M, Harrison Denning K, Dowrick C. The facilitators and challenges of dying at home with dementia: A narrative synthesis. *Palliat Med*. 2018;32(6):1042-1054.
19. Fetherstonhaugh D, McAuliffe L, Bauer M, Shanley C. Decision-making on behalf of people living with dementia: how do surrogate decision-makers decide? *J Med Ethics*. 2017;43(1):35-40.
20. Song MK, Ward SE, Hanson LC, et al. Psychological symptoms and end-of-life decision making confidence in surrogate decision-makers of dialysis patients. *J Nephrol Soc Work*. 2012;36.
21. Lillyman S, Bruce M. Palliative care for people with dementia: a literature review. *Int J Palliat Nurs*. 2016;22(2):76-81.
22. Martinsson L, Lundström S, Sundelöf J. Quality of end-of-life care in patients with dementia compared to patients with cancer: A population-based register study. *PLoS ONE*. 2018;13(7).

CHAPTER 2: REVIEW OF THE LITERATURE

2.1 INTRODUCTION

An extensive literature review was conducted between May 2018 and May 2019 using Pubmed, Cochrane, Ovid, and Scopus. Primary searches were performed using the combination of MeSH terms “dementia,” “palliative care,” “quality of life,” and “patient readmissions.” Other search terms included advanced dementia, Alzheimer’s disease, location of death, caregiver quality of life, end of life care, and palliative medicine. The search was limited to articles written in English. We prioritized clinical studies, systematic reviews, and meta-analyses. Throughout the primary literature search, we extracted additional studies for inclusion from the reference section of previously identified studies included in this review. Together, the data from this comprehensive review support the need for a well-designed randomized controlled trial (RCT) to evaluate the effect of early palliative care on the well-being of those living with advanced dementia.

2.2 PROOF OF CONCEPT - Advanced Dementia & Unmet Palliative Care Needs

Globally, dementia is one of the leading causes of death in older adults. The number of deaths by dementia is expected to increase in the future due to the rapidly expanding population.¹ Dementia dramatically impacts the quality of life of patients through a combination of physical, psychological, and psychosocial factors. The progressive and unpredictable nature of dementia leads to significant cognitive and functional decline, which severely affect each individual’s ability to live independently, maintain relationships, and make medical decisions. One cross-sectional logistic

regression analysis in the US found that decedents with any diagnosis of dementia vs. those with no dementia had a higher prevalence of hearing loss, vision loss, dysphagia, difficulty speaking, pain, weakness, low energy, poor balance and coordination, depression and anxiety (all $p < 0.05$), and subsequent higher symptomatic burden.² As a result, patients with dementia are frequently rehospitalized and exposed to unnecessary or invasive treatments like enteral feeding, blood sampling, antibiotic use, and resuscitation.³ Additionally, these patients receive inadequate symptom control for pain and dyspnea.⁴ For these reasons, individuals with dementia often have a significant reduction in quality of life.

Advanced dementia is characterized by progressive and persistently severe disability during the last year of life. Although estimates of prognosis vary from six months to three years, advanced dementia is as a terminal condition. At this stage, the focus of the majority of the care provided should be palliative, maximizing comfort and quality of life, rather than curative. While palliative care has traditionally focused on patients with cancer, there has been a call worldwide for improved access to palliative care services for all people with life-limiting diseases, including people with dementia.¹

Despite evidence in the literature regarding the devastating impact that advanced dementia has on patients' end-of-life quality, studies show that patients with dementia are receiving different care than people from other chronic diseases.^{1,3-8} One retrospective cohort study of 68,091 decedents found that patients dying from dementia suffered from an extensive burden of symptoms (pain, dyspnea, anxiety, agitation, and delirium) similar to that of patients with cancer.⁷ But, they received less medication for symptoms and seldom had access to specialized palliative care compared to cancer patients (1.3% versus

23.8%; OR 0.059 CI 0.051–0.068; $p < 0.001$).⁷ Similarly, a retrospective cohort study found that patients with dementia of any severity during an acute admission are less likely to be referred to palliative care ($p = 0.007$), to be prescribed palliative medications ($p = 0.017$) and to have caregivers involved in decision making ($p = 0.006$) compared to non-dementia patients.⁹ These discrepancies may be explained by ongoing difficulties in recognizing “end-stage” dementia, and that many patients living with dementia have poor knowledge of or access to advanced care planning resources. Conversely, a retrospective cross-sectional study of all decedents at 146 inpatient facilities within the Veteran Affairs health system over two years found that more patients with cancer and dementia received palliative care consultations (73.5% and 61.4%, respectively) than patients with end-stage renal disease (50.4%), cardiopulmonary failure (46.7%), and frailty (43.7%, all $p < 0.01$).¹⁰

There may also be a lack of understanding of the benefits of palliative care in dementia. An online study found that among caregivers for someone living with dementia, participants equated palliative care with pain management only, and rarely linked palliative care to dementia.⁸ This knowledge gap of the benefits of palliative care may apply to healthcare providers as well. A retrospective cohort study found that the number of referrals of dementia patients to palliative care and hospice varies by physician type.¹¹ Hospitalists were more likely than generalists to refer the patients to palliative care and hospice (AOR 1.17, 95% CI 1.09-1.26), suggesting a difference in palliative medicine education amongst specialties. A population-based survey regarding end-of-life care by physicians found that palliative care services were not used in 64% of people with dementia because it was not deemed meaningful or the providers believed the patient was already receiving sufficient care.⁵ These results suggest a persistent need for

more awareness and studies clarifying the benefit of palliative care to people with dementia.

These reviewed studies demonstrate that further work is required to illuminate ways to improve end-of-life care in this large and growing population. Palliative care represents a feasible and impactful option.

2.3 REVIEW OF EMPIRICAL STUDIES

2.3.1 Palliative Care as an Intervention to Improve Outcomes in Chronic Diseases

Palliative care is a specialty of medicine focused on populations living with chronic diseases to improve patient quality of life through the reduction of symptoms and stress. Specialty palliative care is available in 85% of large hospitals (greater than 300 beds) in the United States.¹² The body of literature on palliative care uses many different outcome measurements. For the purpose of this review, we will focus on clinical trials related to our primary and secondary outcomes of interest: non-institutionalized days, number of readmissions, location of death, and psychological distress of surrogate decision makers.

Many studies in populations of people living with chronic diseases have found that palliative care treatment reduces hospital length of stay and number of readmissions.¹³⁻¹⁸ Surveys suggest that people prefer dying at home because it is generally a therapeutic, calm and respectful environment.⁸ As a result, palliative care empowers patients with the ability to make the choice to die at home if they personally consider that to be the best quality of life and identifies the pathways to achieve that goal.^{3,19} Three recent retrospective cohort studies assessed readmission and length of stay outcomes after an inpatient palliative care consultation (PCC). First, a study of 1,430

patients with any diagnosis of a chronic disease found that patients seen by palliative care had a lower 30-day readmission rate (AOR 0.66, 0.55-0.78; $p < 0.001$).¹³ Another study of 102,746 patients admitted with congestive heart failure found that those receiving an inpatient PCC were less likely to be readmitted for heart failure (9.3% vs. 22.4%, $p < 0.01$) or for any cause (29.0% vs. 63.2%, $p < 0.01$) during the 9-month follow-up period.¹⁵ Finally, a study of 540 general inpatients utilized an early PCC (within 48 hours of admission) and found that patients demonstrate a shorter length of stay (5.08 days $p < 0.05$).¹⁷ Readmissions at 30, 60, and 90 days after a PCC also decreased (61.5%, 47.0%, and 42.1%, respectively). These studies suggest that palliative care decreases number of readmissions and length of stay, and increases time spent out of the hospital.

Palliative care consultations have also demonstrated an effect on patient location of death. A retrospective cohort study assessed the effect of an outpatient PCC in terminally ill cancer patients.¹⁴ The medical team provided PCC at the patient's home including long term care facilities, assisted living, and private homes. Irrespective of age, gender, and type of tumor, patients seen by the palliative home-care team were more likely to die at home, less likely to be hospitalized, and spent fewer days in hospital in the last two months of their life. A related retrospective cohort study involving 16,497 all-cause decedents assessed the effect of inpatient PCC on location of death.²⁰ Patients who received inpatient PCC were less likely to die in a hospital (15% vs. 29%) or intensive care (2% vs. 9%) compared with controls (both, $p < 0.001$). Of those who received a PCC, 51% died at home compared to 41% of those who did not receive an inpatient PCC ($p < 0.001$). These studies demonstrate that a palliative care consultation—whether

inpatient or outpatient—enables terminally ill patients to avoid dying in the acute care setting.

Another important consideration in palliative care is the evaluation of the psychological distress of surrogate decision makers. Facing difficult issues like how to support the patient's right to make autonomous choices and how best to promote a good quality of life for the patient are particularly distressing. Anxiety, depression, and post-traumatic stress are common symptoms experienced by surrogate decision makers.²¹ One study of 120 dialysis patients' surrogates found that experiencing depression and anxiety may predispose them to psychological illness later in life, even after the patient's death.²¹ Likewise, a study comparing bereaved surrogates of palliative cancer patients to the general population demonstrated that surrogate decision makers experience a significantly decreased mental quality of life, general health, and social functioning.²² Interventions to support surrogates are essential so that negative psychological symptoms may be avoided. Two randomized control trials, each studying the effect of PCC on caregivers or surrogates in populations with idiopathic pulmonary fibrosis or advanced cancer, are underway.^{23,24} These studies aim to assess the change in levels of emotional distress between families of these patients who receive palliative care support or not. Palliative care may improve symptoms of psychological distress through support for surrogates in medical decision-making and advance care planning.

Overall, this literature review found that data supports the positive effect of palliative care on outcomes such as length of stay, hospital readmissions, and location of death. All of these outcomes are associated with quality of end-of-life care. More data are needed to support the effect on the psychological burden of surrogate decision makers.

These data encourage the use of palliative care in all patients suffering with a chronic disease.

2.3.2 Palliative Care as an Intervention to Improve Outcomes in Advanced Dementia

Literature supporting the use of palliative care in patients living with dementia is less robust than the literature supporting the use of palliative care in other chronic diseases such as cancer. However, there have been many important studies that will be described here. This portion of the review first describes several foundational studies related to our proposed trial and then details the results of studies more specifically related to our proposed outcomes of interest.

Foundational Studies

A large systematic review conducted by Murphy et al. in 2016 sought to assess the effect of palliative care interventions from trials in advanced dementia, and to report on the range of outcome measures used in the trials.¹ After an extensive review of 1535 RCTs and non-randomized controlled trials, the review concluded that “very little high-quality work has been completed” and “there is insufficient evidence to assess the effect of palliative care interventions in advanced dementia.” The majority of the 1535 identified studies were excluded from this review because they did not assess palliative interventions only, did not include patients with advanced dementia, or did not stage patients with a validated tool. More well designed RCTs are required to further describe how palliative care can best be used to serve this population.

One of the studies included in the Murphy et al. review, a landmark trial by Ahronheim et al. (2000), investigated the effectiveness of a palliative care team

consultation in patients with advanced dementia (FAST 6d or greater) hospitalized for an acute illness.²⁵ This study individually randomized patients over three years to either primary inpatient care team plus palliative care team input, or primary inpatient care team alone. Between the intervention and control groups, mean number of hospitalizations (1.94 versus 1.90; $p=0.92$), average length of stay in days (8.8 versus 9.7; $p=0.46$) and mortality (12 and 12; $p=0.96$) were similar. More patients in the intervention group chose to forgo certain medical treatments, but the results were not statistically significant. Overall, this study noticed trends in favor of palliative care consults, but failed to demonstrate a statistically significant impact in hospitalized patients with advanced dementia.

A more recent RCT was published in January 2019 by Hanson et al. with the objective to study dementia-specific specialty palliative care triggered by hospitalization.¹² This pilot RCT enrolled dyads of persons with late-stage dementia (5-7 on the Global Deterioration Scale [GDS]) and family decision-makers upon admission to the hospital. Like the FAST, the GDS is a staging tool for advanced dementia. The scale values of 5 to 7 represent patients with moderately severe to very severe cognitive impairment. The intervention involved specialty palliative care consultation during hospitalization with post-discharge telephone support by a palliative care nurse practitioner. The control group received usual hospital care with educational material on dementia caregiving. The study found no significant change in hospital and emergency department visits in the 60 days following intervention. While primary outcomes were not met, more intervention families made decisions to avoid rehospitalization (13% vs. 0%; $p = 0.033$), and intervention families were more likely to discuss prognosis (90% vs.

3%; $p < 0.001$) and goals of care (90% vs. 25%; $p < 0.001$). This innovative pilot study found that specialty palliative care consultation specific to late-stage dementia, initiated during hospitalization for acute illness, is feasible and promising for improved outcomes for patient-surrogate dyads.

Some limitations may exist in each of these studies. Both groups of authors recognize that there may have been a more substantial effect size if they had recruited a larger sample population. The generalizability may be limited in each study, as both studies were conducted at a single location. Additionally, family decision makers in the Hanson et al. study were compensated for time to complete the interviews which may have encouraged greater participation than might be observed in real-world clinical practice without compensation. Notably, the Ahronheim et al. study was published in 2000 and may describe a different era of palliative care in medicine than today. Finally, each study demonstrates an opportunity to further clarify the opportune timing of palliative care intervention as neither specified a time for the intervention. Each of these studies lays important groundwork supporting the feasibility of this kind of study, and demonstrates the need to do a larger, multisite study in an integrated healthcare system that can support this broader intervention.

Outcome-specific studies

After reviewing these foundational studies, the remaining literature review will address the efficacy of a palliative care consultation in patients with advanced dementia, specifically regarding outcomes of interest in our proposed trial. These outcomes include length of stay, readmissions, location of death, and psychological distress of surrogate decision makers.

Literature suggests that access to palliative care may reduce patients' time spent institutionalized in a healthcare setting. One retrospective cohort study of dementia patients staged FAST 6d (moderately severe dementia with urinary incontinence) or above found lower acute care use and burdensome transitions near the end-of-life in those who received palliative care consultations.²⁶ Conversely, other studies on length of stay and readmissions are not so clear. The Ahronheim et al. study discussed previously found no significant change in readmissions or average length of stay.²⁵ Likewise, the 2019 Hanson et al. study observed no change in hospital and emergency department visits within 60 days of a palliative care intervention during hospitalization. However, as mentioned above, this same study found that more intervention families made decisions to avoid rehospitalization (13% vs. 0%; $p=0.033$).¹² The evidence suggests that palliative care enables patients to spend more time at home, but consistent significant data is lacking.

Palliative care may reduce exposure to physically and emotionally stressful transitions between places of care at the end of life. Currently, people with dementia tend to die in residential care, in acute hospitals, or at home without palliative interventions.^{1,6} One retrospective cohort study estimated that the incidence of hospital death in those with dementia dying of pneumonia was 47.2%.⁶ The study also concluded that a quarter of those living in long-term care settings died in a hospital. The authors offered that this may suggest shortcomings in the healthcare system in preventing potentially avoidable terminal hospitalizations in a vulnerable population.⁶ This research demonstrates a need to further clarify the impact of palliative care on a critical aspect of end-of-life care: location of death.

It is important to consider the needs of caregivers and surrogate decision makers when discussing palliative care implementation in the advanced dementia population. One systematic review described treatment decision making involving a person with dementia in the acute care setting.²⁷ The study illustrated that surrogates often felt unsupported in making treatment decisions for their loved ones and unsure if palliative care was necessary or important. The review concluded that healthcare practitioners should utilize palliative care as a means to educate both surrogates and providers about PCCs, negotiate a clear role for caregivers and provide them support in decision-making.²⁷ Some studies have sought to further explore decision making for persons with dementia in the acute care setting.

In a cluster RCT from Hanson et al., the effect of a palliative care-based decision aid on end-of-life feeding options for patients with advanced dementia (GDS 7, very severe cognitive decline) was evaluated.²⁸ Intervention surrogates had lower scores for decisional conflict measured on the Decisional Conflict Scale (a questionnaire designed to assess decisional conflict in surrogates, patients and providers) and were more likely than participants in the control group to discuss feeding options with a clinician (RR 1.57, 95% CI 0.93 to 2.64).²⁸ A related pilot RCT randomized patient-caregiver dyads for patients with severe dementia (FAST stage 6d or above) admitted to the hospital emergently to receive a palliative care assessment.²⁹ The palliative care team offered an advanced care planning meeting. The general trend in caregiver distress scores were the highest at baseline, decreased after intervention, and increased again around the time of bereavement. However, attrition precluded statistical comparison of the control and intervention groups. Data from these two studies suggest that palliative medicine-

centered aid may be a possible intervention effective in reducing surrogate psychological distress.

While many existing studies explore the relationship between palliative care and patients living with dementia, there remains a gap in the literature that this proposal may help to fill. Common considerations of limitations in the studies described above include insufficient sample sizes and lack of generalizability. Additionally, the need for randomized controlled trials over observational trials is important to describe a cause-effect relationship between palliative care and outcomes such as length of stay, readmissions, location of death, and psychological distress of surrogate decision makers in the advanced dementia population.

2.4 POTENTIAL CONFOUNDING VARIABLES

As with any clinical trial, there are many confounding variables that may impact the results of this proposed study. These include age, admitting diagnosis, level of frailty, severity of illness, ICU vs. general hospital admission, and the relationship of the surrogate decision maker to the patient. We also anticipate potential for confounding relating to differing dementia etiologies and severity of dementia.

For the purpose of this review, the term dementia is used to incorporate all types of dementias including Alzheimer's disease, Lewy Body, frontotemporal lobe, etc. This is done under the assumption that while the dementia subtypes may follow different disease trajectories, the final stage will include similar challenges in end-of-life care. One retrospective cohort study compared end-of-life care quality indicators between patients with dementia or cancer.⁷ In a secondary analysis, there was no significant difference between Alzheimer's disease and all causes of dementia in outcomes of thirteen end-of-

life care quality indicators.⁷ No other studies comparing the quality of end-of-life care between patients with Alzheimer's disease and other dementia diagnoses have been found in the literature. Dementia etiologies will be detailed in analysis of the baseline characteristics between groups.

This proposed study plans to include patients living with advanced dementia as defined by Functional Assessment Staging Tool (FAST) stage 6d-7f (Appendix F). This proposal focuses on advanced dementia because patients with advanced dementia experience profound decline in cognitive and functional status, and are often not referred to palliative care despite their severe needs. While patients on the scale from 6d to 7f may differ in prognosis, their course of disease may similarly benefit from palliative care intervention. Severity of dementia will be detailed in analysis of the baseline characteristics between groups.

As described in further detail in the methods portion of this proposal, patients with certain comorbidities will be excluded from this study. The study will exclude patients with cancer undergoing active chemotherapy, chronic lung disease on home oxygen, heart failure New York Heart Association (NYHA) class IV, renal failure on dialysis, or end stage liver disease MELD score greater than 30, as these are groups that might otherwise be seen as high risk for unmet PCC and we propose a more homogenous group of dementia patients for this trial. Of note, the two studies discussed earlier that lay the groundwork for this proposal did not exclude patients based on comorbidities.^{12,25} If we are unable to recruit sufficient numbers under these exclusion criteria, it is possible to include these patients and analyze the comorbidities as baseline characteristics to ensure proper randomization and prevent confounding.

2.5 REVIEW OF RELEVANT METHODOLOGY

This portion of the literature review includes a review of methodology that is relevant to the proposed study. A more detailed explanation of the proposed study methods is discussed in Chapter 3.

2.5.1 Study Design

The study setting will be a multisite, integrated healthcare system in the US: the Veterans Affairs (VA) Healthcare System. Study locations include the VA Connecticut Health Care System, VA Western New York Healthcare System, VA Hudson Valley Health Care System, VA NY Harbor Healthcare System, VA Boston Healthcare System, VA Pittsburg Healthcare System, Miami VA Healthcare System, North Florida Veterans Health System, West Texas VA Healthcare System, Central Texas Veterans Healthcare System, VA Puget Sound Healthcare System, and San Francisco VA Healthcare System. This proposal is feasible because all VA sites utilize the same electronic health record and have access to inpatient palliative care teams. The proposed trial is a multicenter design to ensure adequate recruitment and expand generalizability.

The reference standard for clinical research is the randomized controlled trial. RCTs are prospective by definition, as a result they can establish a causal effect between the intervention and primary outcomes. The randomization process helps to prevent bias and confounding within the study sample. Previous RCTs evaluating the relationship between palliative care and outcomes for patients with dementia have utilized random-number generation and a 1:1 allocation to intervention and control groups, as we propose to do in this study.^{12,25} This will help to reduce risk of selection bias.

Due to the nature of a palliative care intervention, blinding either the clinicians or the participants to group assignment is not feasible. This has been well described in the palliative care literature.²⁸ To help prevent performance bias, we propose a cluster randomized trial by hospitalist attending. Cluster designs are also at risk for recruitment bias given that providers were randomized before recruitment of all participants and surrogate dyads.¹ To decrease the risk of detection and interpretive bias, a research assistant blinded to randomization status will gather data and perform data analysis from patients in both arms of the study.

There are two important ethical considerations in this proposed study design. First, it is possible that a primary team caring for a patient may see the need for a palliative care consultation in a patient-surrogate dyad who were randomized to the control group. This dyad should not be denied the opportunity of a palliative care consultation if the clinical judgement of the team makes that determination; this poses a risk for crossover to occur. This would bias our results toward the null hypothesis, and thus, any effect observed would be a conservative estimate of the potential efficacy of the intervention. Second, there is some ethical debate over whether patients should be included in research if they are near the end of life. However, one study on the ethics of research in palliative care found that terminally-ill patients were willing to be enrolled in research studies if this could improve their symptoms and improve the care of future patients.³⁰

2.5.2 Selection Criteria

Patients will be considered for the study if they are aged 50 or older, are hospitalized with an acute illness, have a clinical diagnosis of advanced dementia FAST

6d-7f, and have an eligible surrogate decision maker. Surrogate decision makers are eligible if they are legally authorized representatives for health care decisions and can complete an interview in English.¹² More details on inclusion and exclusion criteria can be found in Chapter 3.

In this study, dementia is defined according to recommendations regarding validated International Classification of Diseases and Related Health Problems, 10th Revision, Clinical Modification (ICD-10-CM) codes for the diagnosis of dementia in an inpatient setting: ICD-10-CM F00, F01, F02, F03, F04, G30, G31 (except G31.2), I69.91, R41 and subgroups.^{5,7,12,31,32} One study on the validity of dementia-related ICD-10 codes examined the concordance of dementia-related ICD codes with textual comments in corresponding medical records.³¹ The study found that an ICD code-based dementia diagnosis had a true positive rate of at least 73%.³¹

ICD-10-CM is the most contemporary coding system at this time, but the switch from ICD-9-CM occurred as recently as 2015. ICD-10-CM uses 69,823 codes, an almost five-fold increase in codes from ICD-9-CM.³³ Consequently, it is essential to know how the transition from ICD-9 to ICD-10 has affected reporting of diseases like dementia. One study done within the VA healthcare system measured chronic condition rates two years before and one year after the transition to ICD-10. The goal was to examine changes in prevalence rates and potential measurement issues for 34 chronic conditions, including dementia and Alzheimer's.³³ Condition prevalence estimates were similar before and after the transition for most conditions. An exception, Alzheimer's disease had more than twice the odds of being measured with ICD-10 compared to ICD-9.³³ This is an important consideration in this study's use of ICD-10-CM dementia coding definitions.

The use and validity of the Functional Assessment Staging Test (FAST) tool has been supported by researchers in the fields of geriatrics and palliative care.^{1,25,34} Briefly, category 6d-e are characterized by urinary and fecal incontinence. The most severe category, 7f, is characterized by the ability to hold up head independently. Please see appendix F for the entire scale.

2.5.3 Intervention

Structure of Intervention:

The palliative care consultation will be conducted by the regular protocol in the VA Healthcare System. The intervention will follow the general guidelines as set by previous research in the field.^{12,25} The consult protocol will address the components listed in Table 1 below.¹² All participating palliative care providers will complete a training prior to trial initiation to ensure a consistent intervention. The palliative care team will also discuss each patients' management with the primary healthcare team in the hospital on a daily basis during admission. The palliative care team may converse with surrogate decision makers via the phone or in person. The control group will be treated by the primary care team without proactive, early input of the palliative care team.

Table 1: Components of a Palliative Care Consultation

Components of a Palliative Care Consult	
<ul style="list-style-type: none"> ○ Stage, prognosis, and trajectory of dementia ○ Assessment and treatment of pain and other physical symptoms ○ Assessment and management of neuropsychiatric symptoms ○ Social support for caregiver stress 	<ul style="list-style-type: none"> ○ Spiritual needs assessment ○ Cultural concerns framing care ○ Goals of care decision-making ○ Key clinical decisions such as feeding options, antibiotic use, and rehospitalization

Timing of Intervention:

While there is growing evidence that people with dementia will benefit from palliative care, there is no consensus among specialists regarding what stage this care should be initiated. Studies have demonstrated that early initiation of palliative care in other populations improves outcomes such as length of stay, hospital readmissions, mortality and quality of life.^{16,17} A survey regarding end-of-life care by physicians found that one reason for failure to refer to palliative care was insufficient time to initiate palliative care.⁵ This study also found that patients dying with cancer were referred to palliative care an average of eight days sooner than patients dying with dementia ($p < 0.001$). This demonstrates that there is still a need to promote awareness of the benefits of early palliative care in patients with dementia. As a result, we propose a palliative care intervention within 72 hours of patient admission to the hospital to ensure enough time for a consultation during admission, and also to allow enough time to contact appropriate surrogates. Practically, this time period may aid in enrolling patients over the weekend when palliative care is not available at most VA locations.

2.5.4 Outcome Measures

The primary outcome of this proposed study is the number of days the patient spent at home (including other facilities like skilled nursing facility or assisted living if defined as home by the patient-surrogate dyad) instead of admitted to a healthcare facility for a health-related problem in the six months following palliative care consultation. This may be simply stated as non-institutionalized days in the six months following intervention. Data on hospital length of stay and number of readmissions reveal trends in

time spent in an institution versus at home after palliative care consultation. This study's novel outcome will more explicitly describe this relationship.

Two proposed secondary outcomes, readmissions and location of death, are regularly used in palliative care research. The length of follow up for these outcomes is not standardized; we will follow up for six months. The other secondary outcome, psychological distress of surrogate decision makers, will be assessed with the Hospital Anxiety and Depression Scale (HAD Scale, or HADS), prior to intervention and at monthly data collection points as per protocol in other studies in this field.²² The HADS is a valid and reliable self-rating scale that measures anxiety and depression in both patients with illness or the general population. The test duration is about 2-5 minutes. The anxiety portion addresses items such as attention, worry, fear, panic, difficulty relaxing, and restlessness.³⁵ The depression portion predominantly measures anhedonia, the inability to experience pleasure from activities usually found enjoyable.³⁵ As suggested by the original HADS paper, there are clear cut-off scores to indicate the severity of symptomatology.^{22,36} A cumulative score (0-21) can be created for each scale. A score of 0-7 is considered normal, a score of 8-11 borderline abnormal, and a score from 11-21 abnormal. In summary, the HADS is a widely used questionnaire that is able to quickly and easily detect psychological distress in populations such as surrogate decision makers for patients living with dementia.

2.5.5 Sample Size

Six retrospective cohort studies and one RCT support the effectiveness of palliative care interventions in reducing hospital length of stay and number of

readmissions, thus enabling patients to spend the final period of their lives at home.

These studies are detailed in the table below.

Table 2: Summary of Studies Supporting Calculation of Sample Size

Author/Year	Study Design/ Sample Size	Study Population	Intervention	Outcome
Bharadwaj¹⁷ 2016	Retrospective cohort, 540	Patients at multihospital healthcare delivery system over one year.	PC consult within 48 hours of admission.	PC services within the first 48 hours of admission demonstrate a shorter LOS (5.08 days). Readmissions at 30, 60, and 90 days after a PC consult decreased (61.5%, 47.0%, and 42.1%, respectively).
Hanson¹² 2019	RCT, 62	Dyads of patient-surrogates inpatient at large hospital	Inpatient PC consult	The study found no significant change in hospital and emergency department visits (intervention vs. control, 0.68 vs. 0.53 transfers per 60 days; $p = 0.415$)
O'Connor¹³ 2015	Retrospective cohort, 1430	Patients at a large urban medical center.	PC consult	Patients seen by PC had a lower 30-day readmission rate-adjusted odds ratio (AOR) 0.66, 0.55-0.78; $p < 0.001$.
Rilof¹⁴ 2014	Retrospective cohort, 402	Patients dying of cancer in 2011.	PC consult.	Patients taken into care by the palliative home-care team were more likely to die at home, less likely to be hospitalized, and spent fewer days in hospital in the last 2 months of their life.
Wiskar¹⁵ 2017	Retrospective cohort, 2287	Patients admitted with HF exacerbations who received inpatient PC consult.	Inpatient PC consult.	Those receiving a PC visit were less likely to be readmitted for HF (9.3% vs. 22.4%, $P < 0.01$) or for any cause (29.0% vs. 63.2%, $P < 0.01$) during the 9-month follow-up period.
Wright¹⁸ 2018	Retrospective cohort, 16439	Cancer decedents in Perth, Australia.	At least 1 mo of community-based PC in the last 6 mo of life.	Fewer unplanned hospitalizations in the last six months of life.
Zalenski¹⁶ 2017	Retrospective cohort, 405	ICU patients screened for PC needs.	PC consult in the ICU.	They had slightly lower 30-day readmissions-(AOR = 0.7; 95% CI 0.5-1.0); not significantly different.

Of note, these studies were primarily conducted on populations other than solely patients living with dementia. One retrospective cohort study of 780 individuals admitted to a geriatric palliative care unit by Lo et. al. sought to answer whether there is a difference between length of stay in individuals admitted with a primary diagnosis of dementia compared to individuals admitted with other noncancer and cancer diagnoses.⁴ They found that individuals with an admission diagnosis of advanced dementia had no difference in the mean length of stay between the three groups.

These studies have found the average number of readmissions and average hospital length of stay to be reduced after palliative care consultations. This supports the *directionality* of our hypothesis. To estimate *effect and sample size*, we looked to one study done by Cassel et. al on the effect of home-based palliative care program on healthcare use and costs. The study found that dementia patients who received proactive palliative care spent a mean number of 0.75 +/- 2.11 days in the hospital per month, as compared to those without palliative care who spent a mean number of 1.68 +/- 2.56 days in the hospital per month between enrollment and death.³⁷ We can extrapolate this data to estimate the mean number of non-institutionalized days in the last six months of life, shown in the table below. The control data is supported by a descriptive study which found that the number of mean hospital days over a period of six months in patients dying with dementia to be 16.5 +/- 0.4.³⁸

Table 3: Literature-supported primary outcome estimate

Calculation	Variable	Intervention Group	Control Group
	Mean # Hospital days/mo	0.75 +/- 2.11	1.68 +/- 2.56
<i>Multiply x 6</i>	Mean # Hospital days/6 mo	4.5 +/- 12.66	10.08 +/- 15.36
<i>180 days - mean # hospital days/6 mo</i>	Mean # days at home/6 mo	175.5 +/- 12.66	169.92 +/- 15.36

The online Open Source Statistics for Public Health calculator was used to estimate the sample size needed for this study with the data from the table above.³⁹ The calculation resulted in a raw sample size of 100 patients per study arm and total sample size of 200. This sample size estimation was conducted for comparing two means; however, we will need to correct this due to the fact that our study will be comparing two medians.⁴⁰ To correct, we will increase our sample size by 15%, increasing the size to

115 patients per arm and 230 patients total. Of note, analysis of means may be appropriate if the distribution of data is normal.

Based on an assumed effect size of 10%, a known positive effect for the primary outcome, a type I error rate of 0.05, a type II error rate of 0.2, and proportional intervention and control groups, a sample size of 230 with 115 subjects per group, will be appropriate (Appendix E).

2.6 CONCLUSION

The information presented in this literature review supports the need for this study proposal on early palliative care intervention in advanced dementia patients admitted acutely to the hospital. There is strong evidence that patients with advanced dementia suffer similar or worse quality of life than other patients with chronic or end-stage diseases. The advanced dementia population would benefit immensely from increased awareness and research on the effective implementation of palliative care to improve quality of life. The proposed study, detailed in Chapter 3, will evaluate a palliative care intervention for patients with advanced dementia and their surrogate decision makers with the ultimate goal of improving patient and surrogate well-being. This project will add to the literature regarding optimal treatment and has the potential to influence clinical practice guidelines on advanced dementia.

2.7 REFERENCES

1. Murphy E, Froggatt K, Connolly S, et al. Palliative care interventions in advanced dementia. *Cochrane Database Syst Rev*. 2016;12:CD011513.
2. Amjad H, Snyder SH, Wolff JL, Oh E, Samus QM. Before Hospice: Symptom Burden, Dementia, and Social Participation in the Last Year of Life. *J Palliat Med*. 2019.

3. Lillyman S, Bruce M. Palliative care for people with dementia: a literature review. *Int J Palliat Nurs*. 2016;22(2):76-81.
4. Lo AT, Karuza J, Berall A, Perri GA. Prevalence of Dementia in a Geriatric Palliative Care Unit. *The American journal of hospice & palliative care*. 2018;35(5):799-803.
5. Beernaert K, Deliëns L, Pardon K, et al. What Are Physicians' Reasons for Not Referring People with Life-Limiting Illnesses to Specialist Palliative Care Services? A Nationwide Survey. *PLoS One*. 2015;10(9):e0137251.
6. Houttekier D, Reyniers T, Deliëns L, Van Den Noortgate N, Cohen J. Dying in hospital with dementia and pneumonia: A nationwide study using death certificate data. *Gerontology*. 2013;60(1):31-37.
7. Martinsson L, Lundström S, Sundelöf J. Quality of end-of-life care in patients with dementia compared to patients with cancer: A population-based register study. *PLoS ONE*. 2018;13(7).
8. McInerney F, Doherty K, Bindoff A, Robinson A, Vickers J. How is palliative care understood in the context of dementia? Results from a massive open online course. *Palliat Med*. 2018;32(3):594-602.
9. Afzal N, Buhagiar K, Flood J, Cosgrave M. Quality of end-of-life care for dementia patients during acute hospital admission: a retrospective study in Ireland. *Gen Hosp Psychiatry*. 2010;32(2):141-146.
10. Wachterman MW, Pilver C, Smith D, Ersek M, Lipsitz SR, Keating NL. Quality of End-of-Life Care Provided to Patients With Different Serious Illnesses. *JAMA Intern Med*. 2016;176(8):1095-1102.
11. Ankuda CK, Mitchell SL, Gozalo P, Mor V, Meltzer D, Teno JM. Association of Physician Specialty with Hospice Referral for Hospitalized Nursing Home Patients with Advanced Dementia. *Journal of the American Geriatrics Society*. 2017;65(8):1784-1788.
12. Hanson LC, Kistler CE, Lavin K, et al. Triggered Palliative Care for Late-Stage Dementia: A Pilot Randomized Trial. *J Pain Symptom Manage*. 2019;57(1):10-19.
13. O'Connor NR, Moyer ME, Behta M, Casarett DJ. The Impact of Inpatient Palliative Care Consultations on 30-Day Hospital Readmissions. *J Palliat Med*. 2015;18(11):956-961.
14. Riolfi M, Buja A, Zanardo C, Marangon CF, Manno P, Baldo V. Effectiveness of palliative home-care services in reducing hospital admissions and determinants of hospitalization for terminally ill patients followed up by a palliative home-care team: a retrospective cohort study. *Palliat Med*. 2014;28(5):403-411.
15. Wiskar K, Celi LA, Walley KR, Fruhstorfer C, Rush B. Inpatient palliative care referral and 9-month hospital readmission in patients with congestive heart failure: a linked nationwide analysis. *J Intern Med*. 2017;282(5):445-451.
16. Zalenski RJ, Jones SS, Courage C, et al. Impact of Palliative Care Screening and Consultation in the ICU: A Multihospital Quality Improvement Project. *J Pain Symptom Manage*. 2017;53(1):5-12 e13.
17. Bharadwaj P, Helfen KM, Deleon LJ, et al. Making the Case for Palliative Care at the System Level: Outcomes Data. *J Palliat Med*. 2016;19(3):255-258.

18. Wright CM, Youens D, Moorin RE. Earlier Initiation of Community-Based Palliative Care Is Associated With Fewer Unplanned Hospitalizations and Emergency Department Presentations in the Final Months of Life: A Population-Based Study Among Cancer Decedents. *J Pain Symptom Manage*. 2018;55(3):745-754 e748.
19. Kalseth J, Theisen OM. Trends in place of death: The role of demographic and epidemiological shifts in end-of-life care policy. *Palliative Medicine*. 2017;31(10):964-974.
20. Khang PS, Wang SE, Liu IA, et al. Impact of Inpatient Palliative Care on Quality of End-of-Life Care and Downstream Acute and Postacute Care Utilization. *J Palliat Med*. 2018;21(7):913-923.
21. Song MK, Ward SE, Hanson LC, et al. Psychological symptoms and end-of-life decision making confidence in surrogate decision-makers of dialysis patients. *J Nephrol Soc Work*. 2012;36.
22. Gotze H, Brahler E, Gansera L, Schnabel A, Gottschalk-Fleischer A, Kohler N. Anxiety, depression and quality of life in family caregivers of palliative cancer patients during home care and after the patient's death. *Eur J Cancer Care (Engl)*. 2018;27(2):e12606.
23. Becker CL, Arnold RM, Park SY, et al. A cluster randomized trial of a primary palliative care intervention (CONNECT) for patients with advanced cancer: Protocol and key design considerations. *Contemp Clin Trials*. 2017;54:98-104.
24. Lindell KO, Nouraie M, Klesen MJ, et al. Randomised clinical trial of an early palliative care intervention (SUPPORT) for patients with idiopathic pulmonary fibrosis (IPF) and their caregivers: protocol and key design considerations. *BMJ Open Respir Res*. 2018;5(1):e000272.
25. Ahronheim JC, Morrison RS, Morris J, Baskin S, Meier DE. Palliative care in advanced dementia: a randomized controlled trial and descriptive analysis. *J Palliat Med*. 2000;3(3):265-273.
26. Miller SC, Lima JC, Intrator O, Martin E, Bull J, Hanson LC. Specialty Palliative Care Consultations for Nursing Home Residents With Dementia. *J Pain Symptom Manage*. 2017;54(1):9-16 e15.
27. Pecanac KE, Wyman M, Kind AJH, Voils CI. Treatment decision making involving patients with dementia in acute care: A scoping review. *Patient Educ Couns*. 2018;101(11):1884-1891.
28. Hanson LC, Carey TS, Caprio AJ, et al. Improving decision-making for feeding options in advanced dementia: a randomized, controlled trial. *Journal of the American Geriatrics Society*. 2011;59(11):2009-2016.
29. Sampson EL, Jones L, Thune-Boyle IC, et al. Palliative assessment and advance care planning in severe dementia: an exploratory randomized controlled trial of a complex intervention. *Palliat Med*. 2011;25(3):197-209.
30. Pautex S, Herrmann FR, Zulian GB. Is research really problematic in palliative care? A pilot study. *J Pain Symptom Manage*. 2005;30(2):109-111.
31. Fujiyoshi A, Jacobs DR, Jr., Alonso A, Luchsinger JA, Rapp SR, Duprez DA. Validity of Death Certificate and Hospital Discharge ICD Codes for Dementia Diagnosis: The Multi-Ethnic Study of Atherosclerosis. *Alzheimer Dis Assoc Disord*. 2017;31(2):168-172.

32. Ernecoff NC, Wessell KL, Gabriel S, Carey TS, Hanson LC. A Novel Screening Method to Identify Late-Stage Dementia Patients for Palliative Care Research and Practice. *J Pain Symptom Manage*. 2018;55(4):1152-1158 e1151.
33. Yoon J, Chow A. Comparing chronic condition rates using ICD-9 and ICD-10 in VA patients FY2014-2016. *BMC Health Serv Res*. 2017;17(1):572.
34. Sampson EL, Candy B, Davis S, et al. Living and dying with advanced dementia: A prospective cohort study of symptoms, service use and care at the end of life. *Palliat Med*. 2018;32(3):668-681.
35. Beekman E, Verhagen A. Clinimetrics: Hospital Anxiety and Depression Scale. *J Physiother*. 2018;64(3):198.
36. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand*. 1983;67(6):361-370.
37. Brian Cassel J, Kerr KM, McClish DK, et al. Effect of a Home-Based Palliative Care Program on Healthcare Use and Costs. *Journal of the American Geriatrics Society*. 2016;64(11):2288-2295.
38. Faes K, Cohen J, Annemans L. Resource Use During the Last 6 Months of Life of Individuals Dying with and of Alzheimer's Disease. *Journal of the American Geriatrics Society*. 2018;66(5):879-885.
39. *Open Source Epidemiologic Statistics for Public Health* [computer program]. 2006.
40. O'Keeffe AG, Ambler G, Barber JA. Sample size calculations based on a difference in medians for positively skewed outcomes in health care studies. *BMC Med Res Methodol*. 2017;17(1):157.

CHAPTER 3: METHODS

3.1 STUDY DESIGN

This study is designed to conduct a multi-centered, prospective, cluster-randomized control trial. We will cluster the intervention group on hospitalist attending only. The trial will take place at participating locations of the VA Healthcare System across the United States. Each site will have a research coordinator enrolling patients, palliative care team implementing the intervention, and research analyst gathering and analyzing data. Due to the nature of the intervention, the patients and providers will not be blinded.

3.2 STUDY POPULATION AND SAMPLING

After obtaining IRB approval at participating sites, participants will be sampled from the population of inpatients with a dementia code (detailed later in this section) and found to have advanced dementia (FAST stage 6d-7f) during interview with the surrogate. Patients and surrogates will be recruited as a dyad. Surrogate decision makers can be designated either formally or informally. Formal appointment of surrogates may be as enduring power of guardianship and/or enduring power of attorney. When no surrogate has been legally appointed, a family member or caregiver may assume the role. Once it is confirmed that the patient meets eligibility criteria for this study (Table 4), the site study investigator or research assistant will explain the study rationale and purpose, as well as provide a detailed explanation of the study risks and benefits to the patient and surrogate decision maker. Each dyad will be enrolled with proper patient and/or surrogate decision maker consent.

Table 4: Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Patient: Age 50+ ICD-10-CM Dementia Code FAST stage 6f-7d Admitted for acute illness Has appropriate SDM Surrogate Decision Maker (SDM): Age 18+ Formally or informally designated as SDM Agreeable to post-discharge follow up via telephone.	Patient: Undergoing active chemotherapy Chronic Lung Disease on home O ₂ NYHA Class IV CKD on Dialysis MELD Score > 30 Unable to identify surrogate Depressed or delirious

Patients admitted to participating VA Healthcare System locations with an acute health issue will be flagged if they have ever received an ICD-10-CM dementia code in the past. In this study, dementia is defined according to recommendations regarding validated ICD-10 codes for the diagnosis of dementia in an inpatient setting.^{1,2} Table 2 below details the ICD-10 codes used to identify candidate dementia cases.

Table 5: Dementia ICD-10-CM Codes

ICD-10-CM Code:	Classification:
F00 and subgroups	Dementia in Alzheimer
F01 and subgroups	Vascular Dementia
F02 and subgroups	Dementia in other diseases classified elsewhere
F03 and subgroups	Unspecified Dementia
F04 and subgroups	Organic amnesic syndrome not induced alcohol and other psychoactive substances
G30 and subgroups	Alzheimer's Disease
G31 and subgroups (Except G31.2)	Other degenerative disease of nervous system, not elsewhere classified. G31.2 is excluded (degeneration of nervous system due to alcohol).
I69.91	Cognitive deficits following unspecified cerebrovascular disease
R41 and subgroups	Other symptoms and signs involving cognitive functions and awareness

3.3 PARTICIPANT PROTECTION AND CONFIDENTIALITY

To receive Yale Institutional Review Board (IRB), Yale Human Investigation Committee (HIC), and Veterans Affairs approval, an application for approval of study design and safety will be submitted. The application must be approved prior to the initiation of any study-related activities. In compliance with the Yale IRB application requirements, participant risk will be reasonable in relation to anticipated benefits. The application will include an Authorization and Consent for Participation in a Research Project 200 FR.1 form. The form will include an invitation to participate in the study, the clinical intervention, potential risks/benefits, appropriate treatment alternatives available outside the study, a confidentiality agreement, and instructions related to subject withdrawal from the study (Appendix A).

If participants do not have the capacity to consent for participation in the proposed study, the identified surrogate decision maker may provide consent. This will likely be the case in most, if not all, patient and surrogate pairs. The Yale HIC Policy 340 (regarding participation of individuals with impaired consent capacity) will be followed.

The research investigators must provide proof of certification after a Health Insurance Portability and Accountability Act (HIPAA) training session. Certificates may be presented to the Yale IRB board as part of the application process. Any personally identifiable information will remain protected under strict HIPAA compliance. All information gathered during this study will be secured on a password-protected computer, and only accessible by approved researchers requiring direct access to the information. Each of the study patient and surrogate pairs will be assigned a 4-digit code associated with their information to help protect their information.

3.4 STUDY VARIABLES AND MEASURES

The following baseline characteristics will be collected from each study participant dyad: patient age (years), sex, race (White, Black, Hispanic, Asian, other), residence prior to admission (home, assisted living, long term care facility, other), whether the patient lives alone or with others, FAST dementia stage, type of dementia, admission diagnosis (Pulm/Pneumonia, other infection, GI, Cardiac, Cerebrovascular, Other), and severity of illness (Charlson Comorbidity Index: predicts ten year survival in patients with multiple comorbidities). Baseline characteristics on surrogate decision makers will also be collected: age (years), sex, relationship to patient (legal guardian, power of attorney, family caregiver, unrelated caregiver, other), and whether they've had a prior history of anxiety or depression.

The dependent variable (primary outcome) to be measured in this study is the number of days the patient spent at home instead of admitted to a healthcare facility for a health-related problem in the six months following palliative care consultation, or simply: non-institutionalized days in the six months following intervention. Home may be defined by the patient-surrogate dyad as either a home, apartment, assisted living, long term care facility, rehab facility or other. These data points will be collected monthly following discharge from the hospital.

Secondary outcomes will include the number of readmissions within the follow-up period, location of patient death among decedents, and psychological distress of surrogate decision makers measured with the HAD Scale. Further explanation of the HAD Scale may be found in Chapter 2 (Appendix D). These data points will be collected monthly for the duration of the study.

3.5 METHODOLOGY

3.5.1 Assignment of Intervention

All participants (patient-surrogate dyads) will be assigned an alpha-numerical identifier through a random number generator. A computer program will then be used to randomly select participants by their alpha-numerical identifiers for the intervention or control group. There will be 1:1 allocation to intervention and control groups. We propose to cluster the randomization by hospitalist attending physician. This will ensure that providers do not care for patients in both the intervention and control groups.

3.5.2 Intervention

As the independent variable in this study, a palliative care team will consult a patient-surrogate dyad within 72 hours of admission to the hospital. The palliative care consult will be conducted per VA Hospital protocol within the scope of what a typical multidisciplinary palliative care team provides by the existing palliative care staff. The initial sixty-minute consultation within 72 hours and subsequent conversations with the palliative care team throughout the hospital admission may include assessment and management of physical, psychological and spiritual symptoms of the person. In conjunction with the surrogate, teams may discuss advanced care planning, including decision-aid interventions for surrogates, transitions between care settings, and education on living and dying with advanced dementia for caregivers.³ In the six month follow up period, palliative care will interact with the patient at least once a week or as needed by the clinical judgement of the team. We may audit this follow up period treatment to assess for similar follow up. The intervention is detailed in Chapter 2. The control group

will receive standard medical care by the primary medical team with input from the palliative care team at the discretion of the attending physician.

3.5.3 Adherence

Due to ethical considerations, a patient randomized to the control group may receive a palliative care consult if needed at the discretion of the attending physician. This may pose a risk of crossover. No adverse events are expected with this intervention. The research analyst will collect data via the chart and phone calls to surrogate decision makers, encouraging ease of surrogate decision maker participation.

3.6 DATA COLLECTION

Patient and surrogate decision maker characteristics will be collected on a data collection form (Appendix B) to assess the aforementioned baseline characteristics. Measurements of the primary and secondary outcomes will be gathered for each participant dyad every month after inpatient palliative care consult for the duration of the study, or until patient drop-out occurs (eg. death). Non-institutionalized days in the six months following intervention, number of readmissions within the follow-up period, location of death among decedents, and psychological distress of surrogate decision makers (using the HAD Scale) will be gathered through electronic medical record chart review and monthly phone calls by trained research assistants to the surrogate decision maker.

3.7 SAMPLE SIZE CALCULATION

Based on an assumed effect size of 10%, a known positive effect for the primary outcome, a type I error rate of 0.05, a type II error rate of 0.2, and proportional intervention and control groups, a sample size of 230 with 115 subjects per group will be

appropriate to detect a sizable effect. See the literature review for an explanation of the calculation, and Appendix E.

3.8 ANALYSIS

All data will be analyzed in an intention to treat approach based on the subjects' initial group allocation. Statistical significance is defined as $p < 0.05$ for all measurements.

Baseline characteristics will be analyzed to ensure limited variability between the treatment and control groups. Categorical variables (sex, race, residence, FAST stage, type of dementia, admission diagnosis, surrogate relationship to patient, surrogate anxiety/depression history) will be compared using a chi-square test and reported as a proportion of the population. Continuous variables (age, length of hospital stay) will be compared using a student t-test and reported as a mean \pm standard deviation. If there is a statistically significant difference in baseline characteristics between the intervention and control groups, a multiple linear or logistic regression will be performed to determine if there is an independent association between these characteristics and the primary outcome.

For the primary outcome, we will use a Whitney U, WR sum analysis to measure median number of days spent at home in the six months following intervention.

Secondary outcomes will be compared as follows. The mean number (or median if data is not normally distributed) of readmissions within the follow-up period for the intervention group will be compared to that of the control group with an independent sample student t-test. The location of death (either home or hospital) among decedents in the intervention group will be compared to that of the control group with a chi-square test. The mean scores on the HAD anxiety and depression sub-scales from surrogate decision makers

from the intervention group will be compared to that of the control group with an independent sample student t-test. The number of surrogates who score higher than or equal to eight on the HAD anxiety and depression sub-scales from the intervention group will be compared to that of the control group with a chi-square analysis.

3.9 TIMELINE AND RESOURCES

This proposed study will occur within the allotted two-year time frame. We will submit our study proposal on January 1, 2019. Two months will be allotted for the IRB approval process. Enrollment will begin by month 3. Participants will be enrolled over the course of the study and followed for data collection until month 18. At month 18, enrollment will stop and data collection will continue for the final 6 months of the study (to ensure six months of follow up for the latest recruits within the allotted two-year time frame). Data analysis and manuscript analysis will be completed once the two-year study has ended.

The study will take place at VA hospitals throughout the US Healthcare System, and the study headquarters will be located at the Yale University School of Medicine Physician Associate Program. The study personnel will include the primary investigator, Dr. Kathleen Akgun, MD and student primary investigator Tori Viveen PA-S II. A dedicated team of research assistants will be employed to recruit participants, gather data via chart review and phone calls throughout the study, and complete data entry. The VA Palliative Care providers have agreed to provide their services within 72 hours of patient admission to patients recruited for this study.

Table 6: Proposed Timeline

Timetable for research proposal by specific aims																									
Month	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	...
Specific Aim																									
IRB/HIC Approval	X	X																							
Open Enrollment/ Recruitment			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X							
Data Collection			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Data Analysis												X	X	X	X	X	X	X	X	X	X	X	X	X	X
Manuscript Prep																		X	X	X	X	X	X	X	X

3.10 REFERENCES

1. Martinsson L, Lundström S, Sundelöf J. Quality of end-of-life care in patients with dementia compared to patients with cancer: A population-based register study. *PLoS ONE*. 2018;13(7).
2. Fujiyoshi A, Jacobs DR, Jr., Alonso A, Luchsinger JA, Rapp SR, Duprez DA. Validity of Death Certificate and Hospital Discharge ICD Codes for Dementia Diagnosis: The Multi-Ethnic Study of Atherosclerosis. *Alzheimer Dis Assoc Disord*. 2017;31(2):168-172.
3. Murphy E, Froggatt K, Connolly S, et al. Palliative care interventions in advanced dementia. *Cochrane Database Syst Rev*. 2016;12:CD011513.

CHAPTER 4: CONCLUSION

4.1 ADVANTAGES AND DISADVANTAGES

Our proposed clinical trial has many advantages as well as some limitations. The use of a randomized, controlled design is a significant advantage as random assignment to an arm of the study will increase the chance that the intervention and control groups exhibit balanced baseline characteristics. This will allow more accurate analysis, minimize bias during the trial, and describe a relationship between palliative care and clinical and patient-and-surrogate-centered outcomes for patients with advanced dementia. Another advantage is that this proposal plans to use a multicentered design, hoping to expand generalizability to a larger portion of patients living with advanced dementia in the United States. This multicenter approach may also aid in the recruitment of a sufficient sample size—a problem that other studies in this body of literature have experienced.

This study proposal has several disadvantages. First, despite using a randomized, controlled design, we will be unable to provide a blinded study due to the nature of the palliative care intervention. Second, there is risk for crossover as the control group may receive palliative care services as needed during the course of their disease progression. Withholding these services in a critically ill population is unethical. Additionally, this study does not address several gaps in the dementia literature that have been identified such as unequal access to palliative care for ethnic minority groups or different types of dementia. Interestingly, the VA tends to serve a population more diverse than the US population at large and may represent a unique setting for this type of study. These may represent opportunities for palliative care studies in the future.

4.2 CLINICAL SIGNIFICANCE

The proposed trial has the possibility of addressing a critical gap in the advanced dementia and palliative care literature. While the study design has its limitations, it may help describe an evidence-based relationship between early palliative care interventions and outcomes for patients with advanced dementia and their surrogate decision makers.

While palliative care is every patient's right, this proposal has highlighted several issues for the person suffering with advanced dementia. These include the need for expanded awareness of the benefits of palliative care in the dementia population, the importance of enabling a patient dying with dementia to avoid admissions to healthcare institutions near the end of life, and the importance of supporting surrogate decision makers through the process of dementia's decline. For a person dying with dementia, palliative care encourages a fundamental right to die with dignity and affirms a person's values and life until the end. As Atul Gawande writes in his novel *Being Mortal*, "Our ultimate goal, after all, is not a good death but a good life to the very end. You may not control life's circumstances, but getting to be the author of your life means getting to control what you do with them."¹

4.3 REFERENCES:

1. Gawande A. *Being mortal : medicine and what matters in the end*. First edition. ed. New York: Metropolitan Books : Henry Holt & Company; 2014.

Appendices

APPENDIX A: Compound Consent Form and Privacy Rule Authorization Form

*CONSENT FOR PARTICIPATION IN A RESEARCH PROJECT
200 FR. 1 (2016-2)
YALE UNIVERSITY SCHOOL OF MEDICINE*

Study Title: Early proactive palliative care in hospitalized patients with advanced dementia at the VA: a research proposal.

Study arms: Palliative Care vs. Usual Care

Principal Investigator(s): Tori Viveen PA-S II, Kathleen Akgun MD

Invitation to Participate and Description of Project

You are invited to participate in a research study designed to look at the effects of palliative care consultation on outcomes in patients living with advanced dementia. You and your surrogate decision maker have been asked to participate because you have been flagged as a person living with advanced dementia.

In order to decide whether or not you wish to be a part of this research study you should know enough about its risks and benefits to make an informed decision. This consent form gives you detailed information about the research study, which a member of the research team will discuss with you. This discussion should go over all aspects of this research: its purpose, the procedures that will be performed, any risks of the procedures, possible benefits and possible alternative treatments.

Description of Procedures

If you and your surrogate decision maker agree to participate in this study, he/she or you will be asked questions relative to your demographics by our study coordinator. These questions will include age, sex, ethnicity, and medical questions relative to advanced dementia. The study coordinator will also review medical records to learn more information about other conditions the patient may have relative to advanced dementia and end-of-life care.

If you and your surrogate decision maker are good candidates for this study, you both will be randomized to either the intervention group or a control group. The intervention group will receive input from the palliative care team in the hospital, while the control group will receive usual care from your primary medical team. The palliative care team will visit you within 72 hours of your admission to the hospital. Randomization occurs through a computer-based system in which you have equal chances of being assigned to the intervention or control group. Once you have been assigned to a group, you will be assigned a unique study code that designates your place in the study. This code will be used to identify you throughout the study.

If you agree to participate in this study, you will be asked to:

- Consent to be randomly assigned to palliative care or usual care
 - Palliative care will involve daily consults while inpatient, and at least weekly consults while outpatient.
- You will be required to answer questions about your demographics
- You agree to monthly phone call conversations with a research assistant after you leave the hospital
- You consent for the research team to access your medical records

A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

You will be told of any significant new findings that are developed during the course of your participation in this study that may affect your willingness to continue to participate.

Risks and Inconveniences

We identify no reasonably foreseeable physical risks, discomforts or inconvenience associated with the study. However, some questions may make you uncomfortable and there is the possible risk of loss of confidentiality. Every effort will be made to keep your information confidential; however, this cannot be guaranteed. A minor inconvenience may be the monthly, repetitive phone calls with a representative from the study.

Benefits

Participation in this study could lead to improved quality of life for the patient with advanced dementia and his/her surrogate decision maker. You will have access to all information collected during this trial which you can give to your medical doctor. Your participation in this trial could also help others suffering with advanced dementia to improve their quality of life and to support their surrogate decision makers.

Economic Considerations

There are no costs associated with this study. All interventions will be provided at no cost. You will be responsible for any co-pays required by your insurance company for your standard treatment and hospitalization at the VA.

Treatment Alternatives/Alternatives

If you decide not to participate in this study, you will continue with usual care during your stay at the hospital. If you are randomized to the control group, you may of course still receive consultation from the palliative care team if you or your primary healthcare provider see it necessary.

Confidentiality

Any identifiable information that is obtained in connection with this study will remain confidential and will be disclosed only with your permission or as required by U.S. or State law. Examples of information that we are legally required to disclose include abuse of a child or elderly person, or certain reportable diseases. When the results of the research are

published or discussed in conferences, no information will be included that would reveal your identity unless your specific consent for this activity is obtained.

Representatives from the Yale Human Research Protection Program, the Yale Human Investigation Committee (the committee that reviews, approves, and monitors research on human subjects) may inspect study records during internal auditing procedures. However, these individuals are required to keep all information confidential.

Voluntary Participation and Withdrawal

Participating in this study is voluntary. You are free to choose not to take part in this study. Refusing to participate will involve no penalty or loss of benefits to which you are otherwise entitled (such as your health care outside the study, the payment for your health care, and your health care benefits). However, you will not be able to enroll in this research study and will not receive study procedures as a study participant if you do not allow use of your information as part of this study.

If you do become a subject, you are free to stop and withdraw from this study at any time during its course. To withdraw from the study, you can call a member of the research team at any time and tell them that you no longer want to take part. This will cancel any future phone calls. The researchers may also withdraw you from participating in the research if necessary.

Withdrawing from the study will involve no penalty or loss of benefits to which you are otherwise entitled. It will not harm your relationship with your own doctors or with the VA Healthcare System.

When you withdraw from the study, no new health information identifying you will be gathered after that date. Information that has already been gathered may still be used and given to others until the end of the research study, as necessary to insure the integrity of the study and/or study oversight.

Questions

We have used some technical terms in this form. Please feel free to ask about anything you don't understand and to consider this research and the consent form carefully – as long as you feel is necessary – before you make a decision.

Authorization

I have read (or someone has read to me) this form and have decided to participate in the project described above. Its general purposes, the particulars of my involvement and possible hazards and inconveniences have been explained to my satisfaction. My signature also indicates that I have received a copy of this consent form.

Name of Patient:_____

Name of Surrogate:_____

Surrogate Signature:_____

Date:_____

Signature of Principal Investigator

Date

or

Signature of Person Obtaining Consent

Date

If you have further questions about this project or if you have a research-related problem, you may contact the Principal Investigators.

If, after you have signed this form you have any questions about your privacy rights, please contact the Yale Privacy Officer at 203-432-5919. If you would like to talk with someone other than the researchers to discuss problems, concerns, and questions you may have concerning this research, or to discuss your rights as a research subject, you may contact the Yale Human Investigation Committee at (203) 785-4688.

Appendix B: Baseline Characteristics Form

Yale SCHOOL OF MEDICINE

Baseline Characteristics Form

This form is to be completed with the assistance of the research assistant. Patients and surrogate decision makers may participate in the process of gathering information as able.

Study ID: _____

Date of Birth: _____

Patient Information

1. What is your age? _____
2. What is your gender?
☐ Male ☐ Female ☐ Other: _____
3. What is your race?
☐ White ☐ American Indian/Alaskan Native ☐ Native Hawaiian/Pacific Islander
☐ Black or African American ☐ Asian ☐ Other
4. Where do you live?
☐ Home ☐ Apartment ☐ Assisted Living ☐ Long term care facility
Do you live alone? ☐ Yes ☐ No
5. FAST Dementia Stage (To be Completed by Research Assistant)
☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6a ☐ 6b ☐ 6c
☐ 6d ☐ 6e ☐ 7a ☐ 7b ☐ 7c ☐ 7d ☐ 7e ☐ 7f
6. Type of Dementia diagnosis:
☐ Alzheimer's ☐ Vascular ☐ Frontotemporal ☐ Lewy Body ☐ Mixed ☐ Other
7. What is the admission diagnosis?
☐ Pulm/Pneumonia ☐ Other infection ☐ GI ☐ Cardiac ☐ Cerebrovascular ☐ Other

Surrogate Decision Maker Information

1. What is your age? _____
2. What is your gender?
☐ Male ☐ Female ☐ Other: _____
3. What is your race?
☐ White ☐ American Indian/Alaskan Native ☐ Native Hawaiian/Pacific Islander
☐ Black or African American ☐ Asian ☐ Other
4. What is your relationship to the patient?
☐ Legal Guardian ☐ POA ☐ Family caregiver ☐ Unrelated caregiver ☐ Other
5. Do you have a history of depression? ☐ Yes ☐ No
6. Do you have a history of anxiety? ☐ Yes ☐ No

Appendix C: Follow-up Data Collection Sheet

Yale SCHOOL OF MEDICINE

Patient-Surrogate Dyad ID Number: _____

	Time of Enrollment	1 months	2 months	3 months	Cont. as needed
Number of Readmissions	N/A				
Length of Stay if admitted (days)	N/A				
Calculated Days at home	N/A				
Location of death (if patient has passed away)	N/A				
Surrogate HADS Depression Score					
Surrogate HADS Anxiety Score					

Appendix D: Hospital Anxiety and Depression Survey

Hospital Anxiety and Depression Scale (HADS)

Tick the box beside the reply that is closest to how you have been feeling in the past week.
Don't take too long over you replies: your immediate is best.

D	A		D	A	
		I feel tense or 'wound up':			I feel as if I am slowed down:
	3	Most of the time	3		Nearly all the time
	2	A lot of the time	2		Very often
	1	From time to time, occasionally	1		Sometimes
	0	Not at all	0		Not at all
		I still enjoy the things I used to enjoy:			I get a sort of frightened feeling like 'butterflies' in the stomach:
0		Definitely as much	0		Not at all
1		Not quite so much	1		Occasionally
2		Only a little	2		Quite Often
3		Hardly at all	3		Very Often
		I get a sort of frightened feeling as if something awful is about to happen:			I have lost interest in my appearance:
	3	Very definitely and quite badly	3		Definitely
	2	Yes, but not too badly	2		I don't take as much care as I should
	1	A little, but it doesn't worry me	1		I may not take quite as much care
	0	Not at all	0		I take just as much care as ever
		I can laugh and see the funny side of things:			I feel restless as I have to be on the move:
0		As much as I always could	3		Very much indeed
1		Not quite so much now	2		Quite a lot
2		Definitely not so much now	1		Not very much
3		Not at all	0		Not at all
		Worrying thoughts go through my mind:			I look forward with enjoyment to things:
	3	A great deal of the time	0		As much as I ever did
	2	A lot of the time	1		Rather less than I used to
	1	From time to time, but not too often	2		Definitely less than I used to
	0	Only occasionally	3		Hardly at all
		I feel cheerful:			I get sudden feelings of panic:
3		Not at all	3		Very often indeed
2		Not often	2		Quite often
1		Sometimes	1		Not very often
0		Most of the time	0		Not at all
		I can sit at ease and feel relaxed:			I can enjoy a good book or radio or TV program:
	0	Definitely	0		Often
	1	Usually	1		Sometimes
	2	Not Often	2		Not often
	3	Not at all	3		Very seldom

Please check you have answered all the questions

Scoring:

Total score: Depression (D) _____ Anxiety (A) _____

0-7 = Normal

8-10 = Borderline abnormal (borderline case)

11-21 = Abnormal (case)

1. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand.* 1983;67(6):361-370.

Appendix E: Sample Size Calculation

Sample Size For Comparing Two Means

Input Data			
Confidence Interval (2-sided)	95%		
Power	80%		
Ratio of sample size (Group 2/Group 1)	1		
	Group 1	Group 2	Difference*
Mean	175.5	169.92	5.58
Standard deviation	12.66	15.36	
Variance	160.276	235.93	
Sample size of Group 1	100		
Sample size of Group 2	100		
Total sample size	200		

*Difference between the means

Results from OpenEpi, Version 3, open source calculator--SSMean

*This is the raw estimate. See literature review for corrected calculation.

1. Dean AG, Sullivan KM, Soe MM. OpenEpi: Open Source Epidemiologic Statistics for Public Health, Version. www.OpenEpi.com, updated 2013/04/06, accessed 2019/05/13.

Appendix F: Functional Assessment Scale

Functional Assessment Scale (FAST)	
1	No difficulty either subjectively or objectively.
2	Complains of forgetting location of objects. Subjective work difficulties.
3	Decreased job functioning evident to co-workers. Difficulty in traveling to new locations. Decreased organizational capacity. *
4	Decreased ability to perform complex task, (e.g., planning dinner for guests, handling personal finances, such as forgetting to pay bills, etc.)
5	Requires assistance in choosing proper clothing to wear for the day, season or occasion, (e.g. pt may wear the same clothing repeatedly, unless supervised.*
6	Occasionally or more frequently over the past weeks. * for the following A) Improperly putting on clothes without assistance or cueing . B) Unable to bathe properly (not able to choose proper water temp) C) Inability to handle mechanics of toileting (e.g., forget to flush the toilet, does not wipe properly or properly dispose of toilet tissue) D) Urinary incontinence E) Fecal incontinence
7	A) Ability to speak limited to approximately ≤ 6 intelligible different words in the course of an average day or in the course of an intensive interview. B) Speech ability is limited to the use of a single intelligible word in an average day or in the course of an intensive interview C) Ambulatory ability is lost (cannot walk without personal assistance.) D) Cannot sit up without assistance (e.g., the individual will fall over if there are not lateral rests [arms] on the chair.) E) Loss of ability to smile. F) Loss of ability to hold up head independently.
*Scored primarily on information obtained from a knowledgeable informant. Psychopharmacology Bulletin, 1988 24:653-659.	

1. Scian SG, Reisberg B. Functional assessment staging (FAST) in Alzheimer's disease: reliability, validity, and ordinality. *Int Psychogeriatr*. 1992;4 Suppl 1:55-69.

Appendix G: DSM-V Dementia-Major Neurocognitive Disorder Criteria

- Evidence of significant cognitive decline from a previous level of performance in one or more cognitive domains:
 - Learning and memory
 - Language
 - Executive Function
 - Complex Function
 - Perceptual-motor
 - Social cognition
- The cognitive deficits interfere with independence in everyday activities
- The cognitive deficits do not occur exclusively in the context of delirium
- The cognitive deficits are not better explained by another mental disorder (eg., major depressive disorder, schizophrenia)

1. *Diagnostic and Statistical Manual of Mental Disorders*. Fifth Edition (DSM-5) ed. Arlington: American Psychiatric Association 2013.

BIBLIOGRAPHY

1. WHO definition of Palliative Care. <http://www.who.int/cancer/palliative/definition/en/>, 2018.
2. Fact Sheet: Aging in the United States – PRB. <https://www.prb.org/aging-unitedstates-fact-sheet/> 2018.
3. *Diagnostic and Statistical Manual of Mental Disorders*. Fifth Edition (DSM-5) ed. Arlington: American Psychiatric Association 2013.
4. Afzal N, Buhagiar K, Flood J, Cosgrave M. Quality of end-of-life care for dementia patients during acute hospital admission: a retrospective study in Ireland. *Gen Hosp Psychiatry*. 2010;32(2):141-146.
5. Ahronheim JC, Morrison RS, Morris J, Baskin S, Meier DE. Palliative care in advanced dementia: a randomized controlled trial and descriptive analysis. *J Palliat Med*. 2000;3(3):265-273.
6. Amjad H, Snyder SH, Wolff JL, Oh E, Samus QM. Before Hospice: Symptom Burden, Dementia, and Social Participation in the Last Year of Life. *J Palliat Med*. 2019.
7. Ankuda CK, Mitchell SL, Gozalo P, Mor V, Meltzer D, Teno JM. Association of Physician Specialty with Hospice Referral for Hospitalized Nursing Home Patients with Advanced Dementia. *Journal of the American Geriatrics Society*. 2017;65(8):1784-1788.
8. Becker CL, Arnold RM, Park SY, et al. A cluster randomized trial of a primary palliative care intervention (CONNECT) for patients with advanced cancer: Protocol and key design considerations. *Contemp Clin Trials*. 2017;54:98-104.
9. Beekman E, Verhagen A. Clinimetrics: Hospital Anxiety and Depression Scale. *J Physiother*. 2018;64(3):198.
10. Beernaert K, Deliëns L, Pardon K, et al. What Are Physicians' Reasons for Not Referring People with Life-Limiting Illnesses to Specialist Palliative Care Services? A Nationwide Survey. *PLoS One*. 2015;10(9):e0137251.
11. Bharadwaj P, Helfen KM, Deleon LJ, et al. Making the Case for Palliative Care at the System Level: Outcomes Data. *J Palliat Med*. 2016;19(3):255-258.
12. Brian Cassel J, Kerr KM, McClish DK, et al. Effect of a Home-Based Palliative Care Program on Healthcare Use and Costs. *Journal of the American Geriatrics Society*. 2016;64(11):2288-2295.
13. Brooksbank M. Palliative care: Where have we come from and where are we going? *Pain*. 2009;144(3):233-235.
14. Clare L, Nelis SM, Quinn C, et al. Improving the experience of dementia and enhancing active life--living well with dementia: study protocol for the IDEAL study. *Health Qual Life Outcomes*. 2014;12:164.
15. Connor SR. Development of hospice and palliative care in the United States. *Omega (Westport)*. 2007;56(1):89-99.
16. *Open Source Epidemiologic Statistics for Public Health* [computer program]. 2006.
17. Ernecoff NC, Wessell KL, Gabriel S, Carey TS, Hanson LC. A Novel Screening Method to Identify Late-Stage Dementia Patients for Palliative Care Research and Practice. *J Pain Symptom Manage*. 2018;55(4):1152-1158 e1151.
18. Faes K, Cohen J, Annemans L. Resource Use During the Last 6 Months of Life of Individuals Dying with and of Alzheimer's Disease. *Journal of the American Geriatrics Society*. 2018;66(5):879-885.

19. Fetherstonhaugh D, McAuliffe L, Bauer M, Shanley C. Decision-making on behalf of people living with dementia: how do surrogate decision-makers decide? *J Med Ethics*. 2017;43(1):35-40.
20. Fujiyoshi A, Jacobs DR, Jr., Alonso A, Luchsinger JA, Rapp SR, Duprez DA. Validity of Death Certificate and Hospital Discharge ICD Codes for Dementia Diagnosis: The Multi-Ethnic Study of Atherosclerosis. *Alzheimer Dis Assoc Disord*. 2017;31(2):168-172.
21. Gawande A. *Being mortal : medicine and what matters in the end*. First edition. ed. New York: Metropolitan Books : Henry Holt & Company; 2014.
22. Gotze H, Brahler E, Gansera L, Schnabel A, Gottschalk-Fleischer A, Kohler N. Anxiety, depression and quality of life in family caregivers of palliative cancer patients during home care and after the patient's death. *Eur J Cancer Care (Engl)*. 2018;27(2):e12606.
23. Hanson LC, Carey TS, Caprio AJ, et al. Improving decision-making for feeding options in advanced dementia: a randomized, controlled trial. *Journal of the American Geriatrics Society*. 2011;59(11):2009-2016.
24. Hanson LC, Kistler CE, Lavin K, et al. Triggered Palliative Care for Late-Stage Dementia: A Pilot Randomized Trial. *J Pain Symptom Manage*. 2019;57(1):10-19.
25. Houttekier D, Reyniers T, Deliens L, Van Den Noortgate N, Cohen J. Dying in hospital with dementia and pneumonia: A nationwide study using death certificate data. *Gerontology*. 2013;60(1):31-37.
26. Jethwa KD, Onalaja O. Advance care planning and palliative medicine in advanced dementia: A literature review. *Psychiatrist*. 2015;39(2):74-78.
27. Kalseth J, Theisen OM. Trends in place of death: The role of demographic and epidemiological shifts in end-of-life care policy. *Palliative Medicine*. 2017;31(10):964-974.
28. Kapo JM, Akgun KM. Integrating Palliative Care Into the Care of Patients With Advanced Lung Cancer. *Cancer J*. 2015;21(5):434-439.
29. Khang PS, Wang SE, Liu IA, et al. Impact of Inpatient Palliative Care on Quality of End-of-Life Care and Downstream Acute and Postacute Care Utilization. *J Palliat Med*. 2018;21(7):913-923.
30. Lillyman S, Bruce M. Palliative care for people with dementia: a literature review. *Int J Palliat Nurs*. 2016;22(2):76-81.
31. Lindell KO, Nouraie M, Klesen MJ, et al. Randomised clinical trial of an early palliative care intervention (SUPPORT) for patients with idiopathic pulmonary fibrosis (IPF) and their caregivers: protocol and key design considerations. *BMJ Open Respir Res*. 2018;5(1):e000272.
32. Lo AT, Karuza J, Berall A, Perri GA. Prevalence of Dementia in a Geriatric Palliative Care Unit. *The American journal of hospice & palliative care*. 2018;35(5):799-803.
33. Martinsson L, Lundström S, Sundelöf J. Quality of end-of-life care in patients with dementia compared to patients with cancer: A population-based register study. *PLoS ONE*. 2018;13(7).
34. McInerney F, Doherty K, Bindoff A, Robinson A, Vickers J. How is palliative care understood in the context of dementia? Results from a massive open online course. *Palliat Med*. 2018;32(3):594-602.
35. Miller SC, Lima JC, Intrator O, Martin E, Bull J, Hanson LC. Specialty Palliative Care Consultations for Nursing Home Residents With Dementia. *J Pain Symptom Manage*. 2017;54(1):9-16 e15.

36. Mitchell SL, Kiely DK, Hamel MB, Park PS, Morris JN, Fries BE. Estimating prognosis for nursing home residents with advanced dementia. *JAMA*. 2004;291(22):2734-2740.
37. Mitchell SL, Teno JM, Kiely DK, et al. The clinical course of advanced dementia. *N Engl J Med*. 2009;361(16):1529-1538.
38. Mogan C, Lloyd-Williams M, Harrison Denning K, Dowrick C. The facilitators and challenges of dying at home with dementia: A narrative synthesis. *Palliat Med*. 2018;32(6):1042-1054.
39. Morrison RS, Siu AL. Survival in end-stage dementia following acute illness. *JAMA*. 2000;284(1):47-52.
40. Murphy E, Froggatt K, Connolly S, et al. Palliative care interventions in advanced dementia. *Cochrane Database Syst Rev*. 2016;12:CD011513.
41. O'Connor NR, Moyer ME, Behta M, Casarett DJ. The Impact of Inpatient Palliative Care Consultations on 30-Day Hospital Readmissions. *J Palliat Med*. 2015;18(11):956-961.
42. O'Hara RE, Hull JG, Lyons KD, et al. Impact on caregiver burden of a patient-focused palliative care intervention for patients with advanced cancer. *Palliat Support Care*. 2010;8(4):395-404.
43. O'Keeffe AG, Ambler G, Barber JA. Sample size calculations based on a difference in medians for positively skewed outcomes in health care studies. *BMC Med Res Methodol*. 2017;17(1):157.
44. Pautex S, Herrmann FR, Zulian GB. Is research really problematic in palliative care? A pilot study. *J Pain Symptom Manage*. 2005;30(2):109-111.
45. Pecanac KE, Wyman M, Kind AJH, Voils CI. Treatment decision making involving patients with dementia in acute care: A scoping review. *Patient Educ Couns*. 2018;101(11):1884-1891.
46. Piers R, Albers G, Gilissen J, et al. Advance care planning in dementia: recommendations for healthcare professionals. *BMC Palliat Care*. 2018;17(1):88.
47. Riolfi M, Buja A, Zanardo C, Marangon CF, Manno P, Baldo V. Effectiveness of palliative home-care services in reducing hospital admissions and determinants of hospitalization for terminally ill patients followed up by a palliative home-care team: a retrospective cohort study. *Palliat Med*. 2014;28(5):403-411.
48. Sachdev PS, Blacker D, Blazer DG, et al. Classifying neurocognitive disorders: the DSM-5 approach. *Nat Rev Neurol*. 2014;10(11):634-642.
49. Sampson EL, Candy B, Davis S, et al. Living and dying with advanced dementia: A prospective cohort study of symptoms, service use and care at the end of life. *Palliat Med*. 2018;32(3):668-681.
50. Sampson EL, Jones L, Thune-Boyle IC, et al. Palliative assessment and advance care planning in severe dementia: an exploratory randomized controlled trial of a complex intervention. *Palliat Med*. 2011;25(3):197-209.
51. Sclan SG, Reisberg B. Functional assessment staging (FAST) in Alzheimer's disease: reliability, validity, and ordinality. *Int Psychogeriatr*. 1992;4 Suppl 1:55-69.
52. Song MK, Ward SE, Hanson LC, et al. Psychological symptoms and end-of-life decision making confidence in surrogate decision-makers of dialysis patients. *J Nephrol Soc Work*. 2012;36.
53. Wachterman MW, Pilver C, Smith D, Ersek M, Lipsitz SR, Keating NL. Quality of End-of-Life Care Provided to Patients With Different Serious Illnesses. *JAMA Intern Med*. 2016;176(8):1095-1102.

54. Wiskar K, Celi LA, Walley KR, Fruhstorfer C, Rush B. Inpatient palliative care referral and 9-month hospital readmission in patients with congestive heart failure: a linked nationwide analysis. *J Intern Med.* 2017;282(5):445-451.
55. Wright CM, Youens D, Moorin RE. Earlier Initiation of Community-Based Palliative Care Is Associated With Fewer Unplanned Hospitalizations and Emergency Department Presentations in the Final Months of Life: A Population-Based Study Among Cancer Decedents. *J Pain Symptom Manage.* 2018;55(3):745-754 e748.
56. Yoon J, Chow A. Comparing chronic condition rates using ICD-9 and ICD-10 in VA patients FY2014-2016. *BMC Health Serv Res.* 2017;17(1):572.
57. Zalenski RJ, Jones SS, Courage C, et al. Impact of Palliative Care Screening and Consultation in the ICU: A Multihospital Quality Improvement Project. *J Pain Symptom Manage.* 2017;53(1):5-12 e13.
58. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand.* 1983;67(6):361-370.